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(54) Title: NOVEL AEROSOL FORMULATION CONTAINING A POLAR FLUORINATED MOLECULE

(57) Abstract: The present invention relates to a stable pharmaceutical aerosol formulation intended for inhalation. The formulation contains an active substance, an aerosol propellant, a polar fluorinated molecule and an excipient. The preferred propellant is HFA 134a or HFA 227 or a mixture thereof.

NOVEL AEROSOL FORMULATION CONTAINING A POLAR FLUORINATED MOLECULE

The present invention relates to a pharmaceutical aerosol formulation for the administration of a pharmaceutically active substance by inhalation.

5 Pressurised metered dose inhalers (pMDI's) are known in the art. Long standing problems with pMDI's containing suspension formulations include creaming of the suspension, coarse drug suspension, drug flocculation and adhesion to dispensing device.

10 It has now surprisingly been found that these problems can be overcome with a novel pharmaceutical formulation containing a polar fluorinated molecule in conjunction with a suitable excipient. The formulations of the invention give rise to improved aerosol drug suspension characteristics, i.e. increase of phase separation times (creaming or sedimentation), production of a finer suspension, reduction of particles adhesion to the can walls and inhibition of particle flocculation.

15 In a first aspect the invention therefore provides a pharmaceutical formulation comprising a drug, an aerosol propellant, a polar fluorinated molecule and an excipient soluble in the polar fluorinated molecule.

20 Suitable drugs which can be used in the formulation of the invention include all drugs that can be administered via the inhalation route, for example steroids, peptides, oligonucleotides, small organic molecules etc., in particular those administered via a pMDI. Such drugs, which are not limited to those for treating respiratory diseases, include those 25 suitable for administration by nasal delivery and nebulised delivery.

In preferred embodiments, the invention provides stable dispersion for the pulmonary or nasal delivery of one or more bioactive molecules, for local or systemic administration, comprising a fluorinated molecule and an excipient in a propellant or propellant mixture.

30 The biocative agent may be selected from any therapeutic or diagnostic agent. For example it may be from the group of antiallergics, bronchodilators, bronchoconstrictors, pulmonary lung surfactants, analgesics, antibiotics, leukotriene inhibitors or antagonists, anticholinergics, mast cell inhibitors, antihistamines, antiinflammatories, antineoplastics, 35 anaesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof.

Examples of specific drugs which can be formulated according to the invention include mometasone, ipratropium bromide, tiotropium and salts thereof, salemeterol, fluticasone propionate, beclomethasone dipropionate, reproterol, clenbuterol, rofleponide and salts, nedocromil, sodium cromoglycate, flunisolide, budesonide, formoterol fumarate dihydrate, 5 SymbicortTM (budesonide and formoterol), ViozanTM, 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide, terbutaline, terbutaline sulphate, salbutamol base and sulphate, fenoterol, 3-[2-(4-Hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propanesulphonamide, 10 hydrochloride. All of the above compounds can be in free base form or as pharmaceutically acceptable salts as known in the art.

Suitable aerosol propellants include those known in the art such as hydrofluoroalkane propellants including 1,1,1,2-tetrafluorethane (P134a) or 1,1,1,2,3,3,3-heptafluoropropane 15 (P227). Preferred propellants include P134a or P227 or a mixture of P134a and P227, in particular a density-matched mixture of the two.

Suitable polar fluorinated molecules include those commercially available from companies such as Apollo chemicals and Fluorochem. Preferably the polar fluorinated molecules are 20 pharmaceutically acceptable and are non-toxic and non-irritant. Suitable polar fluorinated molecules must be miscible in sufficient quantity in the propellant and to be able to solubilise the excipient. The fluorinated molecules are preferably liquid at room temperature, although solids are also possible. Preferably the polar fluorinated molecules are linear, more preferably with a short carbon chain. Most preferably the polar 25 fluorinated molecules have oxygen functionality, i.e. contain an oxygen containing group including fluorinated alcohols, ethers, carboxylic acid, esters, aldehydes and ketones, amines and their mixtures, and any other fluorinated compounds with oxygen based functional groups.

30 Suitable examples of polar fluorinated molecules include:
n Butyl Pentafluoropropionate, Ethyl Perfluoro n-Dodecanoate, Fluorinert (FC-75),
2,2,3,3,3 Pentafluoropropyl Methyl Ether, Methyl Perfluorodecanoate, 2H Perfluoro-
5,8,11-Trimethyl-3,6,9,12-Tetrafluoropropylether, Fluorad (FC-430), 1,1,2,2,
Tetrafluoroethyl 2,2,3,3 Tetrafluoropropylether, 1H,1H,2H,2H Perfluorooctan-1-ol, 4,4,4-
35 Trifluorobutan-1-ol, Fomblin (MF 402), Fomblin (ZDOL), Perfluoroheptanoic Anhydride,
Methyl Perfluoro 2,5,8,11-Tetramethyl 3,6,9,12, Tetraoxapentadecanoate, N,N-Diethyl-
2,3,3,3 Tetrafluoropropionamide, Ethyl 11H-Perfluoroundecanoate, 1H,1H,2H,3H,3H
Perfluoro-1,2-Nonandiol, 1H,1H, Perfluorononan-1-ol,

Aflunox (606, 1406, 2507, 6008, 14013), Allyl Heptafluorobutyrate, Allyl
Heptafluoroisopropyl Ether, Allyl 1,1,2,3,3,3-Hexafluoropropyl Ether, Allyl
Perfluoroheptanoate, Allyl Perfluorooctanoate, Allyl 1H,1H Perfluoroctyl Ether, Allyl
Perfluoropentanoate, 4-Amino-2,2-Difluorobutyric Acid, 2-Amino-3-Fluorobutyric Acid,
5 4-Amino-2-Fluorobutyric Acid, 2-Amino-4-Iminoheptafluoropent-2-ene, 2-Amino-4,4,4-
Trifluorobutyric Acid, 3-Amino-4,4,4-Trifluorobutyric Acid, 1,1-
Bis(diethylamino)tetrafluoro-1-Propene, Bis(heptafluoroisopropyl)ketone,
Bis(hexafluoroisopropyl)maleate, Bis(hexafluoroisopropyl)itaconate, Bis[2-iodo-3-
10 (perfluoroctyl)propyl]adipate, Bis(pefluoroctyl)itaconate, Bis(perfluoroctyl)maleate,
Bis(2,2,2-trifluoroethyl)itaconate, Bis(2,2,2-trifluoroethyl)maleate, 1H,1H-2,5-
Bis(trifluoromethyl)-3,6-Dioxaundecafluorononanol, 3,3-Bis(trifluoromethyl)-3-
Hydroxypropionic Acid, 2,2 Bis (trifluoromethyl) Propionic Acid, n-Butyl-1,1,2,2-
Tetrafluoroethyl Ether, n-Butyl Trifluoroacetate, tert-Butyl Trifluoroacetate,
1,1,1,5,5,6,6,7,7,7-Decafluoro-2,4-Heptanedione, 1H,1H,6H-Decfluorohexan-1-ol, 2H,3H-
15 Decafluoropentane, Diethyl Difluoromalonate, 2,2-Difluoroethanol, 2,2-Difluoroethyl
acetate, 2,2-Difluoroethylalamine, DL-4,4-Difluoroglutamic acid, 2,2-Difluoromalonamide,
Difluoromethyl, 2,2,3,3,3-Pentafluoropropyl Ether, Difluoromethyl 2,2,2-Trifluoroethyl
Ether, Difluoromethyl 2,2,2-Trifluoroethyl Ether, 1,3-Difluoro-2-propanol, Dimethyl,
Hexafluoroglutarate, Dimethyl Octafluoroadipate, Dimethyl Perfluoroazelate, Dimethyl
20 Perfluoro-1,10-decanedicarboxylate, Dimethyl Perfluorosebacate, Dimethyl
Perfluorosuberate, Dimethyl Tetrafluorosuccinate, Dimethyl 2,2,2-Trifluoropropionyl
Carbinol, 4-Ethoxy-1,1,2-Trifluorobut-1-ene, Ethyl 3-Amino-4,4,4-trifluorocrotonate,
Ethyl Ethoxymethylene-3-oxo-4,4,4-trifluorobutyrate, Ethyl 4-Fluoro-3-methyl-2-
pentenoate, Ethyl 2-Fluoropropionate, Ethyl Heptafluorobutyrate, Ethyl
25 Heptafluorobutyrylacetate, Ethyl 3-Hydroxy-4,4,4-trifluorobutyrate, Ethyl 2-Methyl-3-
hydroxy-4,4,4-trifluorobutyrate, Ethyl Pentafluoropropionate, Ethyl Perfluoroheptanoate,
Ethyl Perfluoro-n-dodecanoate including all compounds like C_nF_{2n+1}CO₂CH₂CH₃, n= 4
to 16 (some H substitution possible in the CF chain, and double bonds), Ethyl Perfluoro-n-
dodecanoate, Ethyl 7H-Perfluoroheptanoate, Ethyl Perfluorononanoate, Ethyl 9H-
30 Perfluorononanoate, Ethyl Perfluorooctanoate, Ethyl Perfluoropentanoate, Ethyl 5H-
Perfluoropentanoate, Ethyl 11H-Perfluoroundecanoate, Ethyl 1,1,2,2-Terafluoroethyl
Ether, Ethyl 4,4,4-Trifluorobutyrate, Ethyl 3-(Trifluoromethyl)crotonate, Ethyl 4,4,4-
Trifluoro-3-(trifluoromethyl)crotonate, Fluorinert (FC40, FC430, FC70, FC71, FC72,
FC77, FC84, FC87, FC104, FC6001, FC6003), DL-2-Fluoro-3-alanine, 2-Fluoroethanol,
35 D-Erythro-4-Fluoroglutamic Acid, 2-Fluoroethyl Methacrylate, DL-4-Fluoroglutamic
Acid, L-Erythro-4-Fluoroglutamic Acid, D-Threo-4-Fluoroglutamic Acid, DL-Threo-4-
Fluoroglutamic Acid, L-Threo-4-Fluoroglutamic Acid, DL-Erythro-4-Fluoroflutamine, L-
Erythro-4-Fluoroglutamine, DL-Threo-4-Fluoroglutamine, DL-Erythro-4-

Fluoroisoglutamine, L-Erythro-4-Fluoroisoglutamine, DL-Threo-4-Fluoroisoglutamine, 3-Fluoro-DL-Norleucine, Flutec (PP1, PP2, PP3, PP9, PP10, PP11, PP25, PP50), Fomblin (M, Y (L-Vac), Y (H-Vac), Z15, MF402, ZDOL), Galden (HT70, HT85, HT90, HT100, HT110, HT135, HT200, HT230, HT250, HT270), 1H,1H Heptafluorobutan-1-ol, 1H,1H-
5 Heptafluorobutyl Acetate, Heptafluorobutyramide, Heptafluorobutyric Acid, Heptafluorobutyric Anhydride, 4,4,5,5,6,6,6-Heptafluorohexanoic Acid, 4,4,5,5,6,6,6-Heptafluorohexan-1-ol, 4,4,5,5,6,6,6-Heptafluorohex-2-en-1-ol, Heptafluorosiopropyl Methyl Ether, 1,1,1,3,5,5-Heptafluoropentane-2,4-dione, Heptafluoropenta-2-ol, 2-Heptafluoroproxy-2,3,3,3-tetrafluoropropan-1-ol, Heptafluoropropyl Methyl Ether,
10 Heptafluoropropyl 1,2,2,2-tetrafluoroethyl Ether, Heptafluoropropyl Trifluorovinyl Ether, 2,2,3,4,4,4-Hexafluorobutan-1-ol, 2,2,3,3,4,4-Hexafluorobutan-1-ol, 2,2,3,4,4,4, Hexafluorobutyl Difluoromethyl Ether, 2,2,3,4,4,4-Hexafluorobutyl Methacrylate, Hexafluoroglutaramide, Hexafluoroglutaric Acid, Hexafluoroisopropanol, 1,1,1,3,3,3-Hexafluoroisopropyl Acrylate, mono-Hexafluoroisopropyl Itaconate, mono-
15 Hexafluoroisopropyl Maleate, 1,1,1,3,3,3-Hexafluoroisopropyl methacrylate, Hexafluoroisopropyl Methyl Ether, Hexafluoroisopropylurethane-N-ethyl Methacrylate, Hexafluoroleucine, Hexafluoro-2-methylisopropanol; Hexafluoro-1,5-pentanediol, 3,3,4,5,5,5-Hexafluoropentan-2-ol, 1,1,2,3,3,3-Hexafluoropropyl Ethyl Ether, 1,1,2,3,3,3-Hexafluoropropyl Methyl Ether, 4,4,4,6,6,6-Hexafluoro-4-(trifluoromethyl)hexan-1-ol,
20 4,5,5,6,6,6-Hexafluoro4-(trifluoromethyl) hex-2-enoic Acid, 4,5,5,6,6,6-Hexafluoro-4-(trifluoromethyl) hex-2-en-1-ol, Hexafluoro-DL-valine, Isopropyl Trifluoroacetate, N, Methylbis(hexafluorobutyramide), Methyl Heptafluorobutyrate, Methyl Heptafluoropropyl Ketone, Methyl 2,2,3,3,4,4-hexafluorobutyrate, Methyl 2-hydroxy-2-(trifluoromethyl)pen-4-enoate, N-Methyl-N, methoxytrifluoroacetamide, Methyl
25 Nonafluorobutyl Ether, Methyl Nonafluorobutyl Ketone, Methyl 2,2,3,3,4,4,5,5-octafluoropentanoate, Methyl Pentafluorobut-3-enoate, Methyl Pentafluoropropionate, Methyl Pentafluoropropionylacetate, Methyl Perfluorodecanoate, Methyl Perfluorododecanoate, Methyl Perfluoroheptanoate, Methyl 7H-Perfluoroheptanoate, Methyl Perfluorohexadecanoate, Methyl Perfluoro(2-methyl-3-oxahexanoate), Methyl
30 Perfluorononanoate, Methyl Perfluoroctadecanoate, Methyl Perfluoropentadecanoate, Methyl Perfluorotetradecanoate, Methyl Perfluoro-2,5,8,11-tetramethyl-3,6,9,12-tetraoxapentadecanoate, Methyl Perfluorotridecanoate, Methyl Perfluoroundecanoate, Methyl 2,3,3,3-Tetrafluoropropionate, Methyl Trifluoroacetate, Methyl 4,4,4-trifluoroacetoacetate, 2-Methyl-4,4,4-trifluorobutanol, Methyl 4,4,4,-trifluorocrotonate, Methyl 2-(trifluoromethyl), 3,3,3-trifluoropropionate, Methyl Trifluoropropenoate, Methyl
35 Trifluoropyruvate, (Nonafluoro-n-butyl)epoxide, 2-(Nonafluorobutyl)ethyl acrylate, 2-(Nonafluorobutyl)ethyl methacrylate, 6-(nonafluorobutyl)hexanol, 3-(Nonafluorobutyl)-2-hydroxypropyl Acrylate, 3-(Nonafluoro-n-butyl)prop-2-enol, 3-(Nonafluoro-n-butyl)1,2,-

propenoxide, 1H,1H,2H,2H-Nonafluorohexan-1-ol, 1H,1H-Nonafluoropentan-1-ol,
2,2,3,3,4,4,5,5-Octafluoro-1,6-hexanediol, 2,2,3,3,4,4,5,5-Octafluorohexane-1,6-diacrylate,
2,2,3,3,4,4,5,5, Octafluorohexane-1,6-diamethacrylate, 3,3,4,4,5,5,6,6-Octafluoro-1,8-
octanediol, 1H,1H,1H-Octafluoropenta-1-ol, 2,2,3,3,4,4,5,5 Octofluoro-1,6-hexanediol,
5 1,1,1,2,2-Pentafluorobutan-2-ol, 1,1,1,2,2-Pentafluoro-6,6-dimethyl-3,5-heptadione, 6-
(Pentafluoroethyl)hexan-1-ol, 4,4,5,5,5-Pentafluoropentan-1-ol; 2,2,3,3,3-
Pentafluoropropan-1-ol, Pentafluoropropionaldehyde Hydrate, Pentafluoropropionaldehyde
Methyl Hemiacetal, Pentafluoropropionamide, 2,2,3,3,3-Pentafluoropropyl Acrylate,
2,2,3,3,3-Pentafluoropropyl Methacrylate, 2,2,3,3,3-Pentafluoropropyl Methyl Ether,
10 2,2,3,3,3-Pentafluoropropyl 1,1,2,2-Tetrafluoroethyl Ether, 1H,1H,10H,10H-Perfluoro-
1,10-decanediol, 1H,1H-Perfluorodecan-1-ol, 1H,1H,2H,2H-Perfluorodecan-1-ol,
1H,1H,2H,2H-Perfluorodecanethiol, 1H,1H,2H,2H-Perfluorodecyl Acrylate,
1H,1H,2H,2H-Perfluorodecyl Methacrylate, 3-(Perfluoro-n-decyl)prop-2-enol, 3-
(Perfluoro-n-decyl)-1,2-propenoxide, 1H,1H-Perfluoro-(3,7-dimethyloctan-1-ol), 2H-
15 Perfluoro-(5,8-dimethyl-3,6,9-trioxadodecane), 1H,1H,12H,12H-perfluoro-1,12-
dodecanediol, 1H,1H-Perfluorododecan-1-ol, 1H,1H,2H,2H-Perfluorododecan-1-ol,
1H,1H,2H,2H-Perfluorododecyl Acrylate, 1H,1H,2H,2H-Perfluorododecyl Methacrylate,
7H-Perfluoroheptanal, 7H-Perfluoro-1,1-heptanediol, Perfluoroheptanoic Anhydride,
1H,1H-Perfluoroheptan-1-ol, 1H,1H,7H-Perfluoroheptan-1-ol,
20 Perfluoroheptoxy poly(propyloxy) Acrylate, Perfluoroheptoxy poly(propyloxy)
Methacrylate, 1H,1H,7H-Perfluoroheptyl Methacrylate, 1H,1H-Perfluorohexadecan-1-ol, 3
Perfluorohexy-2-Hydroxypropyl Methacrylate, 2-(Perfluoro-n-hexyl)acetaldehyde
Dimethyl Acetal, 3-Perfluorohexyl-2-hydroxypropyl Acrylate, 3-Perfluorohexyl-2-
hydroxypropyl Methacrylate, 3-(Perfluorohexyl)propan-1-ol, 3-(Perfluoro-n-hexyl)prop-2-
enol, 3-(Perfluoro-n-hexyl)-1,2-propenoxide, 11-(Perfluoro-n-hexyl)undecanol, 11-
25 (Perfluoro-n-hexyl)undec-10-enol, 6, (Perfluorosiopropyl)hexan-1-ol, 3-(Perfluoro-3-
methylbutyl)-2-hydroxy Propyl Acrylate, 3-(Perfluoro-3-methylbutyl)-2-hydroxy Propyl
Methacrylate, 1H,1H,2H,2H-Perfluoro-9-methyldecan-1-ol, 2-(Perfluoro-9-
methyldecyl)ethyl Acrylate, 2H-perfluoro-5-methyl-3,6-dioxanonane, 1H,1H,2H,2H-
30 Perfluoro-11-methyldodecan-1-ol, Perfluoro-(2-methylhept-3-ene-5-one), 1H,1H,2H,2H,
Perfluoro-5-methylhexan-1-ol, 2-(Perfluoro-5-methylhexyl)ethyl Acrylate, 2 (perfluoro-5-
methylhexyl)ethyl Methacrylate3-(Perfluoro-5-methylhexyl)-2-hydroxypropyl Acrylate, 3-
(Perfluor-5-methylhexyl)-2-hydroxypropyl Methacrylate, 1H,1H,2H,2H,-Perfluoro-7-
methylocatn-1-ol, 2-(Perfluoro-7-methyloctyl)ethyl Acrylate, 2-(Perfluoro-7-
35 methyloctyl)ethyl Methacrylate, 6-(Perfluoro-7-methyloctyl)hexanol, 3-(Perfluoro-7-
methyloctyl)-2-hydroxypropyl Acrylate, 3-(Perfluoro-7-methyloctyl)-2-hydroxypropyl
Methacrylate, 1H,1H,2H,3H,3H-Perfluoro-1,2-nonanediol, 1H,1H,9H,9H-Perfluoro-1,9-
nonanediol, 1H,1H-Perfluorononan-1-ol, 1H,1H,9H-perfluorononan-1-ol, 1H,1H,9H-

Perfluoronon-1-ene, 1H,1H,9H-Perfluorononyl Acrylate, 1H,2H,9H-Perfluorononyl Methacrylate, 1H,1H-Perfluoroctadecan-1-ol, 1H,1H,8H,8H-Perfluoro-1,8-octanediol, n-Perfluorooctanoic acid Ammonium Salt, 1H,1H-Perfluoroctan-1-ol, 1H,1H,2H,2H-Perfluoroctan-1-ol, 1H,1H,8H-Perfluoroctan-1-ol, Perfluoroctoxy-poly(isobutoxy)-2-chloropropoxy-1,2-propyl Diacrylate, 2-(Perfluoro-n-octyl)acetaldehyde, 2-(Perfluoro-n-octyl)acetaldehyde Diethyl Acetate, Perfluoroctyl Acrylate, 1H,1H-Perfluoroctyl Acrylate, 1H,1H,2H,2H-Perfluoroctyl Acrylate, 6-(Perfluoroctyl)hexanol, 3-(Perfluoroctyl)-2-hydroxypropyl Acrylate, 3-(Perfluoroctyl)-2-hydroxypropyl Methacrylate, mono-Perfluoroctyl Itaconate, mono-Perfluoroctyl Maleate, 10 Perfluoroctyl Methacrylate, 1H,1H-Perfluoroctyl Methacrylate, 3-(Perfluoroctyl)propanol, 3-(Perfluoroctyl)prop-2-enol, 11-(Perfluoro-n-octyl)undec-10-en-1-ol, 1H,1H,5H,5H-Perfluoropentyl-1,5-dimethacrylate, Perfluoropolyether linear & PFO-XR75, Perfluorosebacic Acid, 1H,1H-Perfluorotetradecan-1-ol, 1H,1H,13H-Perfluorotridecan-1-ol, Perfluoro-2-trifluoromethyl-4-oxanonane, Perfluoro-(3,5,5-trimethylhexanoic)acid, 1H,1H-Perfluoro(3,5,5-trimethylhexan-1-ol), 2H-Perfluoro-(5,8,11-trimethyl-3,6,9,12-tetraoxatetradecane), 1H,1H,2H,3H,3H-Perfluoro-1,2,-undecanediol, Perfluoroundecanoic Acid, 1H,1H-Perfluoroundecan-1-ol, 1H,1H,11H-Perfluoroundecan-1-ol, 1H,1H,11H-Perfluoroundecyl Acrylate, 1H,1H,11H-Perfluoroundecyl Methacrylate, Polyperfluoroethylene glycol Diacrylate, 20 Polyperfluoroethylene glycol Dimethacrylate, Sodium Heptafluorobutyrate, Sodium Pentafluoropropionate, 2,2,3,3-Tetrafluoro-1,4-butanediacrylate, 2,2,3,3-Tetrafluoro 1,4, butanedimethacrylate, 1,1,3,3-Tetrafluorodimethyl Ether, 1,1,2,2-Tetrafluoroethyl 2,2,3,3-tetrafluoropropyl Ether, 1,1,2,2, Tetrafluoroethyl 2,2,2-trifluoroethyl Ether, 1122 Tetrafluoroethyl 222 Trifluoroethyl Ether, 1,2,2,2-Tetrafluoroethyl Trifluoromethyl Ether, 4,5,5,5-Tetrafluoro-4-(heptafluoropropoxy)pentanoic Acid, 4,5,5,5-Tetrafluoro-4-(heptafluoropropoxy)pentan-1-ol, Tetrafluorosuccinic acid, 4,5,5,5-Tetrafluoro-4-(trifluoromethoxy)pentan-1-ol, 4,5,5,5-Tetrafluoro-4-(trifluoromethyl)pentan-1-ol, 4,5,5,5-Tetrafluoro-4-(trifluoromethyl)pent-2-en-1-ol, N-(N-Trifluoroacetyl-L-cysteinyl)glycine Methyl Ester, DL-3,3,3-Trifluoro-2-alanine, 4,4,4-Trifluorobutan-1-ol, 1,1,1-Trifluorobutan-2-one, 4,4,4-Trifluorobutan-2-one, 4,4,4-Trifluorobut-2-en-1-ol, 1,1,2-Trifluoro-2-chloroethyl 2,2,2-trifluoroethyl ether, 4,4,4-Trifluorocrotonamide, 4,4,4-Trifluoro-3,3-dimethoxybutanol, 2,2,2-Trifluoroethanol, 2,2,2-Trifluoroethyl Butyrate, 1,2,2-Trifluoroethyl Trifluoromethyl Ether, 1,1,1-Trifluoro-2,4-hexanedione, Beta-Trifluoromethylcrotonic Acid, DL-2-(Trifluoromethyl)leucine, DL-2-(Trifluoromethyl)norleucine, DL-2-(Trifluoromethyl)norvaline, 2-(Trifluoromethyl)propan-2-ol, 6,6,6-Trifluoronorleucine, 5,5,5-Trifluoronorvaline, 1,1,1-Trifluoropropan-2-ol, 3,3,3-Trifluoropropan-1-ol, 1,1,1-Trifluoro-2-propyl Acetate, 4,4,4-Trifluoro-3-(trifluoromethyl)butan-1-ol, 2-Allyl Hexafluorospiropropanol, Butyl

Difluoroacetate, n-Butyl Pentafluoropropionate, tert-Butyl Pentafluoropropionate, N,N-Diethyl-2,3,3,3-tetrafluoropropionamide, 22 Difluoroethyl Trifluoromethyl Ether, 1-(Ethoxy)nonafluorobutane, 3-Fluoropropan-1-ol, 3H-Heptafluoro-2,2,4,4-tetrahydroxy Pentane, 2,2,3,3,4,4-Hexafluoro-1,5-pentyl Diacrylate, 1,1,2,3,3,3-Hexafluoropropyl 2,2,2-trifluoro Ethyl Ether, Methyl 2,2-Difluoro-3-oxopentanoate, Methyl 2, Methoxytetrafluoropropionate, Methyl Perfluoro-2,5,8,11-tetramethyl-3,6,9,12-tetraoxapentadecanoate, Methyl 3,3,3-Trifluoro-DL-lactate, 3,3,4,4,4-Pentafluorobutan-2-one, Pentafluorodiethyl Ether, Pentafluoroethyl Methyl Ether, 2,2,3,3,3-Pentafluoropropyl Trifluoromethyl Ether, 2-(Perfluoroalkyl)ethanol, 10 Perfluoroallylfluorosulphate, Perfluoro-2,5,8,11,14,17,20-heptamethyl-3,6,9,12,15,18-hexaoxahenelcosanoyl Fluoride, Mono-Perfluoroctyl Itaconate, 2H-Perfluoro-5,8,11,14,17-pentamethyl-3,6,9,12,15,18-hexaoxahenicosane, Perfluoropolyether Dinitrile, Polyfluoropolyethyleneacrylate, Polyfluoropolyethylenemethacrylate, 2,2,2-Trifluoroethyl Trifluoromethyl Ether, Perfluorodecaline, Perfluoroctyl Bromide, di-Chloro-octyl Bromide and 1H,1H,5H Octafluoro-1-pentanol.

Preferably the fluorinated polar molecule is n-Butyl Pentafluoropropionate, Ethyl Perfluoro n-Dodecanoate, Fluorinert (FC-75), 2,2,3,3,3 Pentafluoropropyl Methyl Ether, Methyl Perfluorodecanoate, 2H Perfluoro-5,8,11-Trimethyl-3,6,9,12-Tetrafluoropropylether, 20 Fluorad (FC-430), 1,1,2,2, Tetrafluoroethyl 2,2,3,3 Tetrafluoropropylether, 1H,1H,2H,2H Perfluorooctan-1-ol, 4,4,4 Trifluorobutan-1-ol, Fomblin (MF 402), Fomblin (ZDOL), Perfluoroheptanoic Anhydride, Methyl Perfluoro 2,5,8,11-Tetramethyl 3,6,9,12, Tetraoxapentadecanoate, N,N-Diethyl-2,3,3,3 Tetrafluoropropionamide, Ethyl 11H-Perfluoroundecanoate, 1H,1H,2H,3H,3H Perfluoro-1,2-Nonadiol, 1H,1H, 25 Perfluorononan-1-ol or 1,1,2,2 Tetrafluoroethyl 2,2,2 Trifluoroethyl ether.

Even more preferred fluorinated molecules are 1H,1H,2H,2H Perfluorooctan-1-ol and 1,1,2,2 Tetrafluoroethyl 2,2,2 Trifluoroethyl ether.

30 The excipient for use in the formulation can be a surfactant or a polymer and combinations thereof, copolymers are particularly favoured. The excipient can either be soluble or miscible in the polar fluorinated molecule. Suitable excipients include:

Acrylidone 1005, Crodesta F160, Methoxy PEG Amine, Methoxy PEG carboxymethyl, 4 arms PEG, Cholic acid, MYRJ 52 P, APG-810-XL, APG-1014-XL, Glucapon 215, Glucapon 600, Brij 52, Gum Xanthan, Salicylic Acid, D-Lactose monohydrate, α -Lactose monohydrate, Lecithin egg, Carrageean, Sokalan CO5, Eudragit RLPO, Eudragit RSPO, Eudragit E100, Eudragit S100, Eudragit L100, Poly (DL-lactide coGlycolide), Gantrez S-97

BF, Gantrez AN-119, Gantrez AN-169, Myristic acid, Poly (lactide EO Lactid), Poly (methyl methacrylate- β -ethylene oxide), Lactose, Carboxymethyl cellulose Sodium Salt, 1-O-n-Octyl β D glucopyranoside, AOT DI-CF4H, Dioctyl-sulfosuccinate sodium salt (AOT), Phospholipon 100, Crodesta F10, Crodesta SL 40, APG 3399, Methoxy-PEG-5 DSPE MW 2000, Methoxy-PEG-DSPE MW 5000, N Dodecyl β D Maltoside, N Octyl β D Glucopyranoside, α cyclodextrin, β cyclodextrin hydrate, β cyclodextrin, γ cyclodextrin hydrate, γ cyclodextrin, γ cyclodextrin hydrate, Deoxycholic acid, Taurocholic acid, D-Mannitol, Poly (Methyl Methacrylate), Montanov 202, Montanov 68 EC, n Dodecyl β D Glucopyranoside, N Decyl β D Glucopyranoside, n Decyl β D Maltopyranoside, 10 Glucamate DOE-120, Glucate SS, Glucamate SSE-20, Glucam DOE-120, Glucam P10, Glucam E20, Glucam P20 disteared, Glucam P20, Glucquat 125, Brij 30, Brij 96, Crodasinic LS 30, Crossential L99, Copolymer VC 713, Copolymer 958, Glucopon 650 EC, α Tocopherol, PVP K30, K25 and Plasdone K-29/32, PEG 600 and 1000, Three-Arm Poly (ethylene glycol), 15 lactose based compounds (eg Poly (lactide -co glycolide), Lactitol, Lactose, Cellulose based compounds (e.g. Carboxymethylcellulose, Cellulose, Hydroxypropyl cellulose), Fatty acids (e.g. Castor oil), PEG and derivatives (e.g. Star PEG), Sugar compounds (e.g. Alkyl polyglucosides, Methyl glucosides, Sucrose esters, such as Berol AG6202, Glucopon chemical range, Montanov 68, Montanov 202, Grilloten LSE87, Crodesta chemical range), 20 Poly(ethylene Oxide) compounds (e.g. Hydroxy terminated Three-Arm Polyethylene oxide, Hydroxy terminated Eight-Arm Polyethylene oxide, Carboxy terminated Eight-Arm Polyethylene Oxide, 4 Arms Star Polyethylene Oxide, Poly(methyl methacrylate -b- ethylene oxide), Poly(t-butyl methacrylate -b-ethylene oxide), Poly(lactide-ethylene oxide-lactide) triblock copolymer, Ω -Diacrylonyl terminated poly(lactide-ethylene oxide-lactide) 25 triblock copolymer, Poly(lactone- β -ethylene oxide- β -lactone) triblock copolymer, Poly(ethylene oxide- β -caprolactone), Poly(ethylene oxide- β -propylene oxide) also known as PEO-PPO copolymers, Poly(methyl methacrylate- β -ethylene oxide) also known as PMMA-PEO copolymers)). Further examples include Citric acid, Dibutyl Sebacate, Edetic acid, Glyceryl monooleate & monostearate, Glycofinol, Crodamol chemical range, 30 Maltitol, Maltodextrin, Triglyceride, Polymethacrylate, Polyoxyethylene alkyl ether, Sodium citrate dihydrate, Sorbitol, Mirj and Brij chemical range, Pluronic chemical range, Acrylidone 1005, Fluorinated AOT with different degrees of fluorination, Cholic acid, Copolymer 958, Copolymer VC713, Crossential L99, Crodasinic LS30, AOT Sodium salt, Phospholipon 100H, Salicylic acid, Sokalan CO5, Poly (lactide co glycolide), 35 Poly(ethylene - β - methyl methacrylate), Poly(ethylene - β -2- vinyl pyridine), Poly(ethylene- β -4-vinyl pyridine), Poly(methyl methacrylate - β - sodium acrylate), Poly(methyl methacrylate- β -sodium methacrylate), PEG derivative compounds (Amino acid - PEG, Carboxyl - PEG copolymers, Methoxy PEG amine, Methoxy PEG

carboxymethyl, Branched PEG 4 arms, star PEG, PEG-PLA-PEG triblock copolymer etc...), sugar branched cyclodextrins derivatives, PEO cyclodextrins derivatives, and Dendrimer-PEO-Dendrimer triblock-copolymers.

5 Preferably the excipient is PEG based. Preferred excipients include Methoxy-PEG-DSPE MW 5000, Eudragit E100, Glucamate DOE 120, Methoxy-PEG-DSPE MW 2000, Acrylidone 1005, Crodesta F160, Methoxy PEG Amine, Methoxy PEG carboxymethyl, 4 arms PEG, Cholic acid, MYRJ 52 P, APG-810-XL, APG-1014-XL, Glucopon 215, Glucopon 600, Brij 52, Gum Xanthan, Salicylic Acid, D-Lactose monohydrate, α Lactose monohydrate, Lecithin egg, Carrageean, Sokalan CO5, Eudragit RLPO, Eudragit RSPO, Eudragit E100, Eudragit S100, Eudragit L100, Poly (DL-lactide coGlycolide), Gantrez S-97 BF, Gantrez AN-119, Gantrez AN-169, Myristic acid, Poly (lactide EO Lactid), Poly (methyl methacrylate- β -ethylene oxide), Lactose, Carboxymethyl cellulose Sodium Salt, 1-O-n-Octyl β D glucopyranoside, AOT DI-CF4H, Dioctyl-sulfosuccinate sodium salt (AOT), Phospholipon 100, Crodesta F10, Crodesta SL 40, APG 3399, Methoxy-PEG-DSPE MW 2000, Methoxy-PEG-DSPE MW 5000, N Dodecyl β D Maltoside, N Octyl β D Glucopyranoside, α cyclodextrin, β cyclodextrin hydrate, β cyclodextrin, gamma cyclodextrin hydrate, gamma cyclodextrin, gamma cyclodextrin hydrate, Deoxycholic acid, Taurocholic acid, D-Mannitol, Poly (Methyl Methacrylate), Montanov 202, Montanov 68 EC, n Dodecyl β D Glucopyranoside, N Decyl β D Glucopyranoside, n Decyl β D Maltopyranoside, Glucamate DOE-120, Glucate SS, Glucamate SSE-20, Glucam DOE-120, Glucam P10, Glucam E20, Glucam P20 disteared, Glucam P20, Glucquat 125, Brij 30, Brij 96, Crodasinic LS 30, Crossential L99, Copolymer VC 713, Copolymer 958, Glucopon 650 EC, α Tocopherol, PVP K30, K25 and Plasdone K-29/32, PEG 600 and 1000, Three-Arm Poly (ethylene glycol).

Most preferably the excipient is Methoxy-PEG-DSPE MW 5000, Eudragit E100, Glucamate DOE 120 or Methoxy-PEG-DSPE MW 2000.

30 The grades of fluorinated molecules and excipients mentioned herein are purely indicative and do not limit the scope of this invention. Preferably the fluorinated molecules and excipients are pharmaceutically acceptable.

35 Other ingredients, for example other co-solvents, stabilisers, surfactants, lubricants, excipients, preservatives, buffers, antioxidants, sweeteners, water trapping agents, bulking agents, and taste masking agents may be included in the formulation of the present invention as desired.

The formulation of the present invention may be prepared, for example, by mixing the fluorinated polar molecule with the excipient, then adding the drug powder to the mixture. Propellant is then added to the drug slurry, the formulation obtained is then dispensed in aliquots into specified pMDI which is suitable for nasal or pulmonary drug delivery by any known method, for example under pressure (addition of propellant under pressure) or by cold filling (addition of propellant at a temperature below its boiling point). The pharmaceutically active component may be processed in order to obtain a desired particle size distribution or specific surface properties. For example the pharmaceutically active component may be micronised by conventional methods prior to mixing, or the mixture of pharmaceutically active component may be micronised by conventional methods, after mixing.

Suitably the concentration of the fluorinated polar molecule is from 0.0001 to 55 % weight/weight, more preferably from 0.1 to 25%, and most preferably from 0.3 to 15%.
The concentraration of excipient is suitably from 0.001% to 1%, preferably 0.01 to 1%.

The pMDI device for use with the formulation of the present invention preferably comprises a metal can, for example an aluminium can, closed with a suitable metering valve. Plastic and glass cans can also be used. Suitable cans, coated cans such as cans coated with a fluoropolymer, and metering valves are known in the art.

The pharmaceutical formulations of the present invention are useful for the local or systemic treatment of diseases and may be administered for example via the upper and lower respiratory tract, including by the nasal route. As such the present invention also provides the pharmaceutical aerosol formulation as defined herein for use in therapy; the use of the pharmaceutical aerosol formulation for the manufacture of a medicament for the treatment of diseases via the respiratory tract; and a method for the treatment of a patient in need of therapy, comprising administering to said patient a therapeutically effective amount of the pharmaceutical aerosol formulation of the present invention. It is expected that inflammatory diseases in the respiratory tract, for example asthma, rhinitis, COPD, alveolitis, bronchiolitis and bronchitis can be treated using the present pharmaceutical aerosol formulation.

The pharmaceutical formulation of the present invention is also useful for systemic delivery for many other non-respiratory diseases e.g. cancer, pain control, anaesthesia, infection, vaccinations etc.

In a further aspect the invention provides the use of a polar fluorinated molecule in conjunction with an excipient to reduce deposition and creaming of a pharmaceutical aerosol formulation, and to obtain easily a very fine stable suspension comprising a hydrofluoroalkane propellant having dispersed therein drug particulates.

5

In a further aspect the invention provides a pharmaceutical aerosol as described herein for use in therapy. The invention further provides a method of treatment of a patient in need of therapy comprising administering to said patient a therapeutically effective amount of a pharmaceutical aerosol formulation as described herein. In particular the invention
10 provides a method of treating asthma, rhinitis and COPD.

The invention will now be illustrated in the following, non-limiting, examples.

Selection of Examples

A series of tests were performed to select novel formulation combinations. To select suitable fluorinated compounds, their solubility or miscibility in propellants HFA 134a and 5 HFA 227 were tested (this is a pre-requisite for the fluorinated additive to play a suitable role in the formulation). Subsequently the solubility of selected excipients was tested in one of the fluorinated liquids (1H,1H,2H,2H Perfluorooctan-1-ol abbreviated as 4HPFOH). Finally 9 excipients (Methoxy-PEG-DSPE MW 2000, Methoxy-PEG-DSPE MW 5000, Glucamate DOE 120, Cholic Acid, APG 3399, AOT DI-HCF₆, 1 Octyl β D 10 Glycopyranoside, 4 arms PEG, and Eudragit E100) were tested in the fluorinated liquids that were miscible in the propellant.

The results of this work are reported in the sections below. Adhesion pictures are shown in the Figures.

15

2.1 Miscibility and solubility of Fluorinated molecules in propellants

For a fluorinated compound to be useful in the novel aerosol formulation, it must preferably be fully miscible or soluble in the propellants at the concentration required. This 20 also implies full miscibility in a mixture of the propellants.

The fluorinated chemical was weighed in a clear PET vial. The vial was then crimped, and subsequently pressure filled with one of the propellants until the desired total weight was reached.

25

The miscibility and solubility in HFA 227 and 134a are listed in Table 1. The values in brackets indicate the concentration at which the test was done. Solutions at concentrations below these limits are therefore monophasic. The concentrations quoted are not upper limits. It is perfectly possible for the fluorinated compounds to be miscible or soluble at 30 higher concentrations. In the case of the Fluorad compound (C=9.09%w/w), the liquid was found to be insoluble at 9.09 %w/w. However this does not exclude that it could be miscible at a lower concentration, and therefore still be useful for the purpose of the invention.

35

NAME	Miscibility or solubility	
	HFA-134a	HFA-227
Ethyl Perfluoro n-Dodecanoate	Yes (C<9.24%w/w)	Yes (C<41.15%w/w)
Fluorinert(FC-75)	Yes (C<55.87%w/w)	Yes (C<50.94%w/w)
2,2,3,3,3 Pentafluoropropyl Methyl Ether	Yes (C<42.63%w/w)	Yes (C<33.49%w/w)
Methyl Perfluorodecanoate	Yes (C<42.63%w/w)	Yes (C<39.40%w/w)
2H Perfluoro-5,8,11-trimethyl-3,6,9,12-tetrafluoropropylether	Yes (C<43.49%w/w)	Yes (C<35.36%w/w)
Fluorad(FC-430)	No (C=9.09%w/w)	Yes (C<10.62%w/w)
1,1,2,2-tetrafluoroethyl 2,2,3,3 tetrafluoropropylether	Yes (C<40.30%w/w)	Yes (C<41.72%w/w)
1H,1H,2H,2H Perfluorooctan-1-ol (4HPFOH)	Yes (C<7.30%w/w)	Yes (C<5.17%w/w)
4,4,4 Trifluorobutan-1-ol	Yes (C<4.43%w/w)	Yes (C<4.63%w/w)
Fomblin MF 402	Yes (C<9.96%w/w)	Yes (C<9.93%w/w)
Fomblin ZDOL	Yes (C<9.93%w/w)	Yes (C<10.04%w/w)
Perfluoroheptanoic anhydride	Yes (C<9.89%w/w)	Yes (C<9.13%w/w)
Methyl perfluoro 2,5,9,11-Tetramethyl 3,6,9,12 Tetraoxapentadecanoate	Yes (C<10.37%w/w)	Yes (C<8.90%w/w)
N,N-diethyl-2,3,3,3 tetrafluoropropionamide	Yes (C<9.96%w/w)	Yes (C<9.2%w/w)
Ethyl 11H-Perfluoroundecanoate	Yes (C<4.93%w/w)	Yes (C<4.43%w/w)
1H,1H,2H,3H,3H Perfluoro-1,2-nonandiol	Yes (C<4.84%w/w)	Yes (C<3.71%w/w)
1H,1H, Perfluorononan-1-ol	Yes (C<4.55%w/w)	Yes (C<4.15%w/w)
n-Butyl Pentafluoropropionate	Yes	Yes

	(C=11.93%w/w)	(C=10.96%w/w)
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Table 1: Miscibility or solubility of fluorinated molecules in propellants

The molecules listed in the chemicals list that do not appear in the following table did not show a solubility commensurate with the other compounds, therefore have not been included in this example section. However, they could still be used within the scope of this invention at a lower concentration range and cannot be excluded as potential systems.

2.2 Solubility of selected excipients in 4HPFOH

10 The second test carried out was to evaluate the solubility (or miscibility in the case of liquid samples) of some excipients in 4HPFOH.

15 The excipients were weighed in glass vials with a screw-on plastic cap. 4HPFOH was added at the required concentration, and the vial sealed with Teflon tape and the screw-on cap. The sample was sonicated and heated to quicken the solubilisation of the excipient. The vial was then allowed to cool down. Observations were subsequently made to assess their solubility (see Table 2 for results).

2.3 Solubility of a range of excipients in Fluorinated systems

20 The last test performed to determine a suitable list of excipients was to assess the solubility of some of the previous excipients in the miscible or soluble fluorinated liquids. Methoxy-PEG-DSPE MW 2000, Methoxy-PEG-DSPE MW 5000, Glucamate DOE 120, Eudragit E100, Cholic Acid, APG 3399, DI-HCF6, 1 Octyl β D Glycopyranoside, and 4 arms PEG were chosen for this purpose.

25 The solubilities were determined by weighing the excipient in a glass vial, adding the fluorinated liquid by weight and sealing the vial with Teflon tape and a screw-on cap. The samples were then heated and sonicated to speed up dissolution and allowed to cool down. Visual observations were made on the cold samples. The concentration of the solutions was 1 %w/w (unless otherwise stated). Therefore, compounds that are recorded as insoluble, are effectively insoluble at 1 %w/w, but could have a lower solubility. The choice of the 1 %w/w limit is arbitrary.

35 The observations on the solubilities are listed in Table 3, 4 and 5 below. Compounds which are soluble can be used as excipients in the novel formulation. For instance in the case of Methoxy-PEG-DSPE MW 2000, 5 fluorinated molecules can be used in

conjunction with the excipient at a concentration of at least 1 %w/w, and at lower concentrations for the 3 other fluorinated molecules.

Name	Concentration %w/w	Solubility or miscibility
Arlacel P135 USA	1.00	Yes
4 arms PEG	1.02	Yes
Brij 30	1.06	Yes
Brij 52	0.99	Yes
Brij 96	1.2	Yes
Cholic acid	0.11	Yes
Crossential L99	1.21	Yes
Deoxycholic acid	0.90	Yes
DI-CF4H	0.11	Yes
DI HCF2	0.98	Yes
DI HCF6	0.95	Yes
Dioctyl-sulfosuccinate sodium salt	0.096	Yes
Dodecytrimethyl Ammonium Bromide	1.00	Yes
Eudragit E100	0.99	Yes
Eudragit RSPO	1.01	Yes
Glucamate DOE-120	1.16	Yes
Glucam E20	1.24	Yes
Glucam P20 disteared	1.18	Yes
Glucam P20	1.31	Yes
Glucquat 125	1.12	Yes
Methoxy PEG Amine	1	Yes
Methoxy PEG Propionic Acid	1.02	Yes
Methoxy PEG carboxymethyl	0.99	Yes
Methoxy-PEG-DSPE MW 2000	1.45	Yes
PEG-600	1.17	Yes
PEG 1000	0.98	Yes
MYRJ 52 P	0.99	Yes
N Octyl beta D Glucopyranoside	0.11	Yes
Nonyltrimethyl Ammonium Bromide	0.96	Yes
PVP K-25	0.95	Yes
PVP K-30	1	Yes
Plasdone K-29/32	1.08	Yes

Three-Arm Poly (ethylene glycol)	0.99	Yes
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Table 2: Solubility of selected excipients in 4HPFOH

	Methoxy-PEG-DSPE MW 2000	Methoxy-PEG-DSPE MW 5000	Glucamate DOE 120
Fluorad	No	Yes	Yes
1,1,2,2-tetrafluoroethyl 2,2,3,3-tetrafluoropropylether	Yes	Yes	Yes
Fomblin MD 402	Yes	Yes	Yes
Fomblin ZDOL	Yes	Yes	No
Perfluoroheptanoic anhydride	No	Yes	Yes
Methyl perfluoro 2,5,9,11-Tetramethyl 3,6,9,12-Tetraoxapentadecanoate	Yes	No	Yes
N,N-diethyl-2,3,3,3-tetrafluoropropionamide	No	No	Yes
1,1,2,2 Tetrafluoroethyl 2,2,2-Trifluoroethyl ether	Yes	Yes	Yes

5 Table 3 Solubility of excipients in Fluorinated systems at 1 %w/w

	Cholic Acid	APG 3399	DI-HCF ₆
Fluorad	No	No	Yes
1,1,2,2-tetrafluoroethyl 2,2,3,3 tetrafluoropropylether	No	No	No
Fomblin MD 402	No	No	Yes
<i>Fomblin ZDOL</i>	No	No	No
Perfluoroheptanoic anhydride	Yes	Yes	Yes
Methyl perfluoro 2,5,9,11-Tetramethyl 3,6,9,12 Tetraoxapentadecanoate	Yes	No	Yes
N,N-diethyl-2,3,3,3 tetrafluoropropionamide	No	No	Yes
1,1,2,2 Tetrafluoroethyl 2,2,2 Trifluoroethyl ether	No	No	Yes (0.1 %w/w)

Table 4 Solubility of excipients in Fluorinated systems at 1 %w/w, unless otherwise stated

5

	1 Octyl β D Glycopyranoside	4 arms PEG	Eudragit E100
Fluorad	No	No	No
1,1,2,2-tetrafluoroethyl 2,2,3,3 tetrafluoropropylether	Not tested	Yes	Yes
Fomblin MD 402	Yes	Yes	Yes
Fomblin ZDOL	Yes	Yes	Yes
Perfluoroheptanoic anhydride	Yes	Yes	Yes
Methyl perfluoro 2,5,9,11-Tetramethyl 3,6,9,12 Tetraoxapentadecanoate	No	Yes	No
N,N-diethyl-2,3,3,3 tetrafluoropropionamide	No	Yes	Yes
1,1,2,2 Tetrafluoroethyl 2,2,2 Trifluoroethyl ether	No	Yes	Yes

Table 5 Solubility of excipients in Fluorinated systems at 1 %w/w

From these results, it is possible to devise suitable excipient combinations that will form the novel formulation.

10

3 Examples selected

3.1 List of examples and controls

15 At least 29 novel formulations can be counted from the results in the previous tables, and many more can be elaborated from the previous lists of chemicals. The following combinations were especially assessed:

20

- 1- Budesonide with Methoxy-PEG-DSPE MW 5000 and 4HPFOH in HFA 227
- 2- Budesonide with Methoxy-PEG-DSPE MW 5000 and 4HPFOH in HFA 134a

- 3- Formoterol Fumarate Dihydrate with Methoxy-PEG-DSPE MW 5000 and 4HPFOH in HFA 227
- 4- Formoterol Fumarate Dihydrate with Methoxy-PEG-DSPE MW 5000 and 4HPFOH in HFA 134a
- 5- Budesonide with Eudragit E100 and 4HPFOH in HFA 227
- 6- Budesonide with Glucamate DOE 120 and 4HPFOH in HFA 227
- 7- Budesonide with Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227
- 8- Formoterol Fumarate Dihydrate with Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227
- 9- Terbutaline Sulphate with Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227
- 10- 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide, with Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227
- 11- Formoterol Fumarate Dihydrate with Glucamate DOE 120 and 1,1,2,2 Tetrafluoroethyl 2,2,2 Trifluoroethyl ether in HFA 227

A range of control samples were prepared to compare directly with the novel formulations,
20 these were:

- 1- Formoterol Fumarate Dihydrate in HFA 227
- 2- Formoterol Fumarate Dihydrate in HFA 134a
- 3- Formoterol Fumarate Dihydrate with PEG 1000 and PVP K25 in a HFA 227 and 134a mix.
- 4- Terbutaline Sulphate in HFA 227
- 5- Terbutaline Sulphate in HFA 134a
- 6- Terbutaline Sulphate with PEG 600 and PVP K30 in HFA 227
- 7- Budesonide in HFA 227
- 8- Budesonide in HFA 134a
- 9- Budesonide with PEG 1000 and PVP K25 in HFA 227
- 10- 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide, in HFA 227
- 11- 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide, in HFA 134a

12- 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-
N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide,
with PEG 600 and PVP K30 in HFA 227

5 All drug material used was micronised.

3.2 Samples preparation

Samples for adhesion and creaming tests were prepared in clear PET vials fitted with a continuous valve. The excipient and fluorinated molecule were mixed and the drug was weighed into the vial. The mixture of fluorinated molecule and excipient was then added to the drug. Once the continuous valve was manually crimped, the propellant was transferred through the valve under pressure to the desired weight. The samples were sonicated for at least 15 minutes, and left to stand for equilibration for up to 12 hours, before observations were made. The samples were then assessed and kept under standard laboratory conditions.

Samples for sizing were prepared in a similar fashion in 12 ml aluminium cans. The cans were then pierced and their content transferred in the measuring cell.

Examples 5 to 11 were prepared at 6 different concentrations to study the influence of the components concentrations.

3.3 Samples concentrations

The examples concentrations can be found below.

Example 1

Budesonide: 0.125 %w/w
Methoxy-PEG-DSPE MW 5000: 0.320 %w/w
4HPFOH: 31.7 %w/w
HFA 227: to 100 %w/w

Example 2

Budesonide: 0.174 %w/w
Methoxy-PEG-DSPE MW 5000: 0.286 %w/w
4HPFOH: 28.4 %w/w
HFA 134a: to 100 %w/w

Example 3

Formoterol Fumarate Dihydrate: 0.154%w/w
Methoxy-PEG-DSPE MW 5000: 0.320 %w/w
4HPFOH: 32.2 %w/w

HFA 227: to 100 %w/w

Example 4

Formoterol Fumarate Dihydrate: 0.220 %w/w

Methoxy-PEG-DSPE MW 5000: 0.317 %w/w

4HPFOH: 31.5 %w/w

HFA 134a: to 100 %w/w

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Example 5

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6 suspensions were prepared

Sample number	Concentration in HFA 227 of: (%w/w)		
	Budesonide	Eudragit E 100	4HPFOH
5.1	0.250	0.151	17.7
5.2	0.245	0.055	6.38
5.3	0.234	0.545	11.5
5.4	0.251	0.183	2.97
5.5	0.264	1.28	20.8
5.6	0.253	1.12	11.3

Example 6

6 suspensions were prepared

Sample number	Concentration in HFA 227 of: (%w/w)		
	Budesonide	Glucamate DOE-120	4HPFOH
6.1	0.262	0.166	18.3
6.2	0.267	0.062	6.88
6.3	0.255	1.12	11.3
6.4	0.264	1.33	21.2
6.5	0.262	0.569	12.1
6.6	0.256	0.192	3.05

Example 7

6 suspensions were prepared

Sample number	Concentration in HFA 227 of: (%w/w)		
	Budesonide	Methoxy-PEG-DSPE MW 2000	4HPFOH
7.1	0.239	0.193	17.1
7.2	0.260	0.078	6.9
7.3	0.249	0.966	11.1
7.4	0.25	1.13	20.0
7.5	0.26	0.519	12.1
7.6	0.255	0.172	3.06

Example 8

6 suspensions were prepared

Sample number	Concentration in HFA 227 of: (%w/w)		
	Formoterol Fumarate Dihydrate	Methoxy-PEG-DSPE MW 2000	4HPFOH
8.1	0.017	0.174	17.3
8.2	0.0174	0.069	6.85
8.3	0.0169	1.04	11.9
8.4	0.0174	0.171	3.04
8.5	0.0172	0.521	12.0
8.6	0.0176	1.19	21.1

Example 9

6 suspensions were prepared

Sample number	Concentration in HFA 227 of: (%w/w)		
	Terbutaline Sulphate	Methoxy-PEG-DSPE MW 2000	4HPFOH
9.1	0.282	0.165	16.4
9.2	0.312	0.047	4.7
9.3	0.288	0.71	8.2
9.4	0.299	1.154	20.9
9.5	0.295	0.51	11.8
9.6	0.294	0.169	3.06

Example 10

6 suspensions were prepared

Sample number	Concentration in HFA 227 of: (%w/w)		
	3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl] propansulphonamide,	Methoxy-PEG-DSPE MW 2000	4HPFOH
10.1	0.043	0.209	18.5
10.2	0.045	0.082	7.2
10.5	0.043	1.021	11.7
10.6	0.043	1.163	20.7
10.7	0.043	0.521	12.1
10.8	0.042	0.170	3.03

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Example 11

6 suspensions were prepared

Sample number	Concentration in HFA 227 of: (%w/w)		
	Fomoterol Fumarate Dihydrate	Glucamate DOE-120	1,1,2,2-tetrafluoroethyl-2,2,2-trifluoroethyl ether
11.1	0.017	0.063	6.98
11.2	0.017	0.159	18.4
11.3	0.016	0.198	3.16
11.4	0.016	0.587	12.1
11.5	0.017	1.10	12.1
11.6	0.017	1.3	22.2

Control 1

Formoterol Fumarate Dihydrate: 0.0167 %w/w

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HFA 227: to 100 %w/w

Control 2

Formoterol Fumarate Dihydrate: 0.0167 %w/w

HFA 134a: to 100 %w/w

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Control 3

Formoterol Fumarate Dihydrate: 0.0167 %w/w
PEG 1000: 0.1 %w/w
PVP K25: 0.001 %w/w
HFA 227: 25 %w/w
5 HFA 134a: to 100 %w/w

Control 4

Terbutaline Sulphate: 0.300 %w/w
HFA 227: to 100 %w/w

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Control 5

Terbutaline Sulphate: 0.3 %w/w
HFA 134a: to 100 %w/w

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Control 6

Terbutaline Sulphate: 0.299 %w/w
PEG 600: 0.03 %w/w
PVP K30: 0.005 %w/w
HFA 227: to 100 %w/w

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Control 7

Budesonide: 0.260 %w/w
HFA 227: to 100 %w/w

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Control 8

Budesonide: 0.259 %w/w
HFA 134a: to 100 %w/w

Control 9

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Budesonide: 0.259 %w/w
PEG 1000: 0.3 %w/w
PVP K25: 0.001 %w/w
HFA 227: to 100 %w/w

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Control 10

3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide: 0.427 %w/w
HFA 227: to 100 %w/w

Control 11

3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide: 0.428 %w/w
HFA 134a: to 100 %w/w

Control 12

3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide: 0.428 %w/w
PEG 600: 0.3 %w/w
PVP K30: 0.0025 %w/w
HFA 227: to 100 %w/w

15 4 Assessment of examples

The novel formulation is especially useful to reduce drug adhesion to the can walls, reduce phase separation times and keep the suspension finely dispersed. Therefore 3 tests were performed: assessment of can wall adhesion, evaluation of creaming or sedimenting rates and sizing of the dispersion. The results were compared with the characteristics of the control samples.

Further tests were carried out to quantify the solubility of the drugs in the fluorinated liquids (the example chosen was 4HPFOH) and to check the degradation of the drugs in 4HPFOH.

4.1 Assessment of the extent of drug adhesion

The assessment of the adhesion of drugs to the can walls was done visually and recorded with a digital camera. The samples prepared in PET vials were observed after a couple of days storage. Their were shaken to enable re-dispersion of the creamed or sedimented layer. At this stage it is important to note that samples prepared with HFA 227 will tend to cream and can show some drug adhesion, whereas samples prepared with HFA 134a tend to sediment and because of it show very little adhesion in the head space. The PET vials were offset against a black background and in some cases allowed to settle before a picture was taken. The level of drug adhesion can be seen on the ring across the vial. The absence of a ring means no adhesion. Adhesion pictures can be found as Figures for the range of

samples prepared. Control samples with reference photographs have been collated as Figures.

The pictures are strong evidence of the benefits of the novel formulation. Two types of drug adhesion can be listed. Firstly, head space adhesion, where the particles are spread in the whole head space area (e.g. control 6). Secondly, adhesion at the propellant-gas interface, which will be referred to as ring adhesion (e.g. example 7.4). In all the controls, both types of adhesion were present. In the novel formulations however, the first kind of adhesion had disappeared in all but cases 5.6, 7.2, 10.2 and 10.6. Even in these cases, its extent was greatly limited. The ring adhesion did exist in some of the examples, but was very faint (e.g. 7.2 and 7.4).

The samples prepared with HFA 134a were on average better than the ones prepared with HFA 227. As mentioned before this is mostly due to the density difference. If the particles are not at the interface, and remain wetted in the liquid, they are not likely to adhere in the head space and form a dry ring or surface coating.

It is also interesting to note that for the 134a samples the novel formulation forms a milky suspension, i.e. a fine suspension, compared to the controls that tend to be coarser (see the grains in controls 2 and 3 for examples). Furthermore, the novel formulations are more stable than the controls as can be seen from the milky appearance of most of the examples. The creaming time for these samples was longer than the time required to set the vial and take the photograph (~ couple of minutes). This was not the case in many of the controls.

Budesonide examples 1, 2, 5, 6 and 7 must be compared with controls 7, 8 and 9 (Budesonide samples). For all the examples the novel formulation reduces drastically the amount of drug adhesion to the wall of the can. In all cases, except examples 5.6 and 7.2, there was virtually no drug on the can wall. Even in the case of examples 5.6 and 7.2, the adhesion was much less than in the control samples. There were instances where a small ring of particles was seen on the can wall, but even this was minimal compared to the controls.

Formoterol Fumarate Dihydrate examples 3, 4, 8 and 11 must be compared with controls 1, 2 and 3. Terbutaline Sulphate examples in series 9 must be compared with controls 4, 5 and 6. 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide examples in series 10 must be compared with control 10, 11 and 12. All these systems showed drastically improved performance over their respective control samples, similar to that described for Budesonide.

4.2 Assessment of the phase separation kinetics of the novel formulation

The phase separation kinetics of the novel formulation was assessed visually and with the OSCAR technique (Optical Suspension Characterisation). The OSCAR technique records the turbidity of a sample at two different heights as a function of time. Samples can be studied in situ, in the clear PET vials.

Photographic pictures of selected samples were taken at regular intervals to provide evidence of the slow phase separation kinetics. Samples prepared in HFA 227 creamed, whereas samples prepared in HFA 134a sedimented due to the density difference between the particles and the propellants.

Drug suspensions with no added stabilisers take a few seconds to a few minutes to be fully destabilised. The novel formulation however takes a much longer time to phase separate. It takes on average a couple of hours to form a separate solid phase layer. This is a significant improvement over the performance of other HFA formulations, and one of the major advantages of this novel formulation.

Examples 1, 2, 3 and 4 were studied with the OSCAR technique. In all 4 cases, the onset of detectable creaming was in excess of half an hour. For example 4, it is in excess of 3 hours. This is beyond the time scale usually observed in other formulations, in particular with the control samples, where creaming happens within a few minutes.

The other examples were studied visually. Pictures were recorded for all samples just after shaking and one hour after shaking. The picture titled "after shaking" are to be understood as pictures taken within one minute to one minute and a half after shaking of the first vial of the series. The systems were stable at one hour, and remained so well beyond that limit, extending to a couple of days in some instances. The control samples however had much reduced stability and on average creamed within half an hour after shaking. The level of instability was dependent on the concentration of additives. All suspensions had improved stability properties in the range of concentrations studied.

4.3 Assessment of the fineness of the novel formulation

Selected novel formulations were sized with a Mastersizer X in situ to demonstrate the absence of flocculation. The Mastersizer X is a laser light diffraction sizing apparatus developed by Malvern. A pressure cell assembly was adapted to be able to perform suspension sizing in propellant. Samples were prepared in 12 ml Aluminium cans fitted with a continuous valve, as described before in the creaming and adhesion section. These cans were then pierced and their content transferred in the measuring chamber with a purpose designed can piercer. 4 drugs were studied, Formoterol Fumarate Dihydrate, Budesonide, Terbutaline Sulphate and 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide. All drugs were micronised. They were formulated with Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227. In addition, Formoterol Fumarate Dihydrate was sized in Glucamate DOE-120 and 1,1,2,2-tetrafluoroethyl-2,2,2-trifluoroethyl ether in HFA 227. The results could then be compared with sizing results of the same drugs in reference HFA formulations. The sizing results have been summarised in the tables below.

Formoterol Fumarate Dihydrate samples

Formoterol Fumarate Dihydrate was sized in 2 examples of the novel formulation. The first one is based on the combination Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227. The second one is based on the combination Glucamate DOE-120 and 1,1,2,2-tetrafluoroethyl-2,2,2-trifluoroethyl ether in HFA 227. The HFA formulation used as a reference was based on a PEG 1000 and PVP K25 mixture in a HFA 134a and HFA 227 blend. Processing of the sizing data was done using the Mie theory. The refractive indices values necessary in the Mie theory were either known (for the 1st novel formulation) or approximated from the pure propellant values (2nd novel formulation and reference HFA formulation). The experimental concentrations are listed in Table 6.1, and the sizing results in Table 6.2.

1 st Novel Formulation	2 nd Novel Formulation	Reference HFA formulation
Methoxy-PEG-DSPE	Glucamate	PEG 1000 – 0.099 %w/w
MW 2000 – 0.171 %w/w	DOE-120 – 1.25 %w/w	PVP K25 – 0.00099 %w/w
4HPFOH – 3.053 %w/w	1,1,2,2-tetrafluoroethyl-2,2,2-trifluoroethyl ether – 21.3 %w/w	FFD – 0.0167 %w/w
FFD – 0.0174 %w/w	FFD – 0.049 %w/w	HFA 134a – 75.12 %w/w
HFA 227 to 100 %w/w	HFA 227 to 100 %w/w	HFA 227 – 24.77 %w/w

30 Table 6.1 Concentrations of Formoterol Fumarate Dihydrate (FFD) samples sized with the

Mastersizer X

Sample	D(v,0.1)	D(v,0.5)	D(v,0.9)	D[4,3]	D[3,2]	Peaks	Span
1 st novel Formulation	1.27	2.2	3.52	2.35	1.93	1	1.022
2 nd novel Formulation	0.90	2.52	5.24	2.86	1.76	1	1.725
Reference HFA formulation	3.99	9.95	116.2	35.5	8.49	2	11.28

5 Table 6.2 Sizing results for the novel formulations and the reference HFA formulation of Formoterol Fumarate Dihydrate (FFD). Dimensions are expressed in μm . Span is [D(v,0.9)- D(v,0.1)]/ D(v,0.5).

10 The sizing results show that micronised FFD formulated in either new formulations has a narrower size distribution than in the reference HFA formulation, and the particles have a smaller average size. This is because in the novel formulation particles can exist as individual particles and not as clusters. Furthermore the novel formulations are monodisperse. This will have some effect on the performance of the pMDI, and it is expected that the ex-valve dose should be finer as well. A finely dispersed suspension is a 15 good indicator of efficient suspending agents. The suspensions are well and truly stabilised by the added excipients.

Budesonide samples

20 Budesonide formulations were sized. The novel formulation was based on the combination Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227. The reference sample was prepared with a PEG 1000 and PVP K25 mixture in HFA 227. Processing of the sizing data was done using the Mie theory. The refractive indices values necessary in the Mie theory were either known (novel formulation) or approximated from the pure propellant values (reference formulation). The experimental concentrations are listed in 25 Table 7.1, and the sizing results on Table 7.2.

Novel Formulation	Reference HFA formulation
Methoxy-PEG-DSPE	PEG 1000 – 0.299 %w/w
MW 2000 – 0.173 %w/w	PVP K25 – 0.001 %w/w
4HPFOH – 3.095 %w/w	Budesonide – 0.256 %w/w
Budesonide – 0.253 %w/w	
HFA 227 to 100 %w/w	HFA 227 to 100 %w/w

Table 7.1 Concentrations of Budesonide samples sized with the Mastersizer X

Sample	D(v,0.1)	D(v,0.5)	D(v,0.9)	D[4,3]	D[3,2]	Peaks	Span
Novel Formulation	0.53	2.13	3.68	2.20	1.30	1	1.479
Reference HFA formulation	7.33	33.5	87.5	41.7	15.1	1	2.395

Table 7.2 Sizing results for the novel formulation and the reference HFA formulation of Budesonide. Dimensions are expressed in μm . Span is $[D(v,0.9) - D(v,0.1)] / D(v,0.5)$.

As for FFD, the sizing results show that micronised Budesonide formulated in the new formulation has a narrower size distribution than in the reference formulation, the particles have a smaller average size, and the size distribution is monodisperse.

Terbutaline sulphate samples

2 Terbutaline sulphate samples were sized. The novel formulation was based on the combination Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227. The reference sample was prepared with a PEG 600 and PVP K30 mixture in HFA 227. Modelisation of the sizing data was done using the Mie theory. The refractive indices values necessary in the Mie theory were either known (novel formulation) or approximated from the pure propellant values (reference formulation). The experimental concentrations are listed in Table 8.1, and the sizing results on Table 8.2.

Novel Formulation	Reference HFA formulation
Methoxy-PEG-DSPE	PEG 600 – 0.03 %w/w
MW 2000 – 0.1743 %w/w	PVP K30 – 0.005 %w/w
4HPFOH – 3.1126 %w/w	Terbutaline
Terbutaline	Sulphate – 0.0612 %w/w
Sulphate – 0.0831 %w/w	
HFA 227 to 100 %w/w	HFA 227 to 100 %w/w

Table 8.1 Concentrations of Terbutaline Sulphate samples sized with the Mastersizer X

Sample	D(v,0.1)	D(v,0.5)	D(v,0.9)	D[4,3]	D[3,2]	Peaks	Span
Novel Formulation	1.46	3.96	2.73	4.53	2.73	1	1.696
Reference HFA formulation	5.68	13.6	40.4	23.1	10.6	1	2.543

Table 8.2 Sizing results for the novel formulation and the reference HFA formulation of Terbutaline Sulphate. Dimensions are expressed in μm . Span is $[D(v,0.9) - D(v,0.1)]/D(v,0.5)$.

As for FFD and Budesonide, the sizing results show that micronised Terbutaline sulphate formulated in the new formulation has a narrower size distribution than in the reference formulation, the particles are centred on a smaller average size, and the size distribution is monodisperse.

3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide samples

Two 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide samples were sized. The novel formulation was based on the combination Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227. The reference sample was prepared with a PEG 600 and PVP K30 mixture in HFA 227. Modelisation of the sizing data was done using the Mie theory. The refractive indices values necessary in the Mie theory were either known (novel formulation) or approximated from the pure propellant values (reference formulation). The experimental concentrations are listed in Table 9.1, and the sizing results on Table 9.2.

Novel Formulation	Reference HFA formulation
Methoxy-PEG-DSPE	PEG 600 – 0.2941 %w/w
MW 2000 – 0.1743 %w/w	PVP K30 – 0.0025 %w/w
4HPFOH – 3.1126 %w/w	3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide, – 0.1009 %w/w
3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide, – 0.0831 %w/w	HFA 227 to 100 %w/w
HFA 227 to 100 %w/w	

Table 8.1 Concentrations of 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide samples sized with the Mastersizer X.

Sample	D(v,0.1)	D(v,0.5)	D(v,0.9)	D[4,3]	D[3,2]	Peaks	Span
Novel Formulation	1.53	3.14	39.9	10.6	2.76	2	12.23
Reference HFA formulation	5.9	22.2	136.3	42.1	12.9	2	5.860

Table 8.2 Sizing results for the novel formulation and the reference HFA formulation of 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide. Dimensions are expressed in μm . Span is $[D(v,0.9) - D(v,0.1)] / D(v,0.5)$.

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As for FFD, Budesonide and Terbutaline sulphate, the sizing results show that micronised 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide formulated in the new formulation has a narrower size distribution than in the reference formulation, the particles have a smaller average size. Although the size distribution has in this case 2 peaks, the peak centred on 90 μm could be due to the approximation of the imaginary part of the medium refractive index, and may not be representative of the sample. It is this shoulder peak that leads to the high span value. Despite this results, the size distribution is still narrower and smaller than in the reference formulation.

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4.4 Further tests: solubility of drug compounds in the novel formulation

This invention is concerned with the formulation of pMDI suspensions, but does not exclude the possibility of the formulation of a solution. Although most drug compounds are insoluble in the fluorinated systems, in some instances it is possible to solubilise the drug. Solubility tests were carried out on 4 different drugs in 4HPFOH: Formoterol Fumarate Dihydrate, Budesonide, Terbutaline Sulphate and 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]-propansulphonamide.

Drug suspensions were prepared in sealed glass vials by weight. The suspensions were then allowed to rest over a couple of day to reach equilibrium. They were firstly assessed optically, and in the case of a possible solubility by UV-vis spectroscopy. The solutions were then filtered with 0.2 µm PTFE filters and studied by UV-Vis spectroscopy between 280 nm and 350 nm. A range of suspensions were prepared, to be able to reach saturation levels. Calibration curves were then drawn by plotting the absorbance as a function of concentration. The inflexion point at which the slope of the calibration plot changed was taken as the solubility limit. The experiment was carried out at least 3 times for each drug.

Formoterol Fumarate Dihydrate, Terbutaline Sulphate and 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]-propansulphonamide are insoluble in 4HPFOH. Suspensions of the corresponding drug were observed optically at C= 0.1 ppm(w/w). At this concentration, particles were visible in the bulk of the solution. Their respective solubilities are therefore less than 0.1 ppm(w/w). I.e. the compounds can be considered as insoluble. Budesonide, however, is soluble in 4HPFOH. Its solubility limit measured by UV-Vis Spectroscopy is between 0.219 %w/w and 0.246 %w/w.

4.5 Further tests: stability of drug compounds in the novel formulation

The stability of Formoterol Fumarate Dihydrate and Budesonide in 4HPFOH were tested and compared with their stability in ethanol.

4 solutions were prepared in glass vials sealed with Teflon tape: Formoterol in 4HPFOH, Formoterol in ethanol, Budesonide in 4HPFOH and Budesonide in ethanol. The concentrations of Formoterol solutions were 0.792 %w/w in 4HPFOH and 1.365 %w/w in ethanol. The concentrations of Budesonide were 0.9315 %w/w in 4HPFOH and 1.215 %w/w in ethanol.

After 3 weeks storage, the levels of total impurity levels in excess of 0.01 % in the Formoterol solutions were 0.782 % for the ethanol solution, and 0.245 % in 4HPFOH. In the case of Budesonide, the levels of impurities were 0.23 %w/w in ethanol and 0.14 %w/w in 4HPFOH.

The impurities come from the degradation of the drug molecule in pure solvent. The total level of impurities in the fluorinated system was therefore up to 3 times less than in ethanol. Drug compounds are therefore more stable in the novel formulation than in other pMDI formulations that use co-solvents. This is yet another distinct advantage of this novel formulation.

Explanation of Figures

Figures 1 – 58 show adhesion pictures for the samples prepared for the examples and controls as follows:

Figure	Example	Figure	Example	Figure	Example
1	1	21	7.5	41	11.1
2	2	22	7.6	42	11.2
3	2	23	8.1	43	11.3
4	4	24	8.2	44	11.4
5	5.1	25	8.3	45	11.5
6	5.2	26	8.4	46	11.6
7	5.3	27	8.5	Figure	Control
8	5.4	28	8.6	47	1
9	5.5	29	9.1	48	2
10	5.6	30	9.2	49	3
11	6.1	31	9.3	50	4
12	6.2	32	9.4	51	5
13	6.3	33	9.5	52	6
14	6.4	34	9.6	53	7
15	6.5	35	10.1	54	8
16	6.6	36	10.2	55	9
17	7.1	37	10.5	56	10
18	7.2	38	10.6	57	11
19	7.3	39	10.7	58	12
20	7.4	40	10.8		

Claims

- 5 1. A pharmaceutical formulation comprising a drug, an aerosol propellant, a polar fluorinated molecule and an excipient.
- 10 2. A pharmaceutical formulation as claimed in claim 1 for administration via the lung or nose.
- 15 3. A pharmaceutical aerosol formulation as claimed in claim 1 or 2 wherein the drug is selected from the group of antiallergics, bronchodilators, bronchoconstrictors, pulmonray lung surfactants, analgesics, antibiotics leukotrine inhibitors or antagonists, anticholinergics, mast cell inhibitors, antihistamines, antiinflammatories, antineoplastics, anaesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof.
- 20 4. A pharmaceutical aerosol formulation as claimed in claim 1 to 3 wherein the drug is selected from budesonide, formoterol, Symbicort™ (budesonide and formoterol), Viozan™, 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propansulphonamide, terbutaline, salbutamol base and sulphate, fenoterol, or 3-[2-(4-Hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propanesulphonamide and pharmaceutically acceptable salts thereof.
- 25 5. A pharmaceutical aerosol formulation as claimed in any one of claims 1 to 4 wherein the propellant is a fluorinated molecule.
- 30 6. A pharmaceutical aerosol formulation as claimed in any one of claims 1 to 5 wherein the propellant is HFA 134a or HFA 227 or a mixture of HFA 134a and HFA 227.
- 35 7. A pharmaceutical aerosol formulation as claimed in claim 1 to 6 wherein the polar fluorinated molecule is liquid at room temperature.
8. A pharmaceutical aerosol formulation as claimed in claim 1 to 7 wherein the polar fluorinated molecule is selected from:
n Butyl Pentafluoropropionate, Ethyl Perfluoro n-Dodecanoate, Fluorinert (FC-75),

2,2,3,3,3 Pentafluoropropyl Methyl Ether, Methyl Perfluorodecanoate, 2H Perfluoro-
5,8,11-Trimethyl-3,6,9,12-Tetrafluoropropylether, Fluorad (FC-430), 1,1,2,2,
Tetrafluoroethyl 2,2,3,3 Tetrafluoropropylether, 1H,1H,2H,2H Perfluorooctan-1-ol, 4,4,4
Trifluorobutan-1-ol, Fomblin (MF 402), Fomblin (ZDOL), Perfluoroheptanoic Anhydride,
5 Methyl Perfluoro 2,5,8,11-Tetramethyl 3,6,9,12, Tetraoxapentadecanoate, N,N-Diethyl-
2,3,3,3 Tetrafluoropropionamide, Ethyl 11H-Perfluoroundecanoate, 1H,1H,2H,3H,3H
Perfluoro-1,2-Nonandiol, 1H,1H, Perfluorononan-1-ol,
Aflunox (606, 1406, 2507, 6008, 14013), Allyl Heptafluorobutyrate, Allyl
Heptafluoroisopropyl Ether, Allyl 1,1,2,3,3,3-Hexafluoropropyl Ether, Allyl
10 Perfluoroheptanoate, Allyl Perfluorooctanoate, Allyl 1H,1H Perfluorooctyl Ether, Allyl
Perfluoropentanoate, 4-Amino-2,2-Difluorobutyric Acid, 2-Amino-3-Fluorobutyric Acid,
4-Amino-2-Fluorobutyric Acid, 2-Amino-4-Iminoheptafluoropent-2-ene, 2-Amino-4,4,4-
Trifluorobutyric Acid, 3-Amino-4,4,4-Trifluorobutyric Acid, 1,1-
Bis(diethylamino)tetrafluoro-1-Propene, Bis(heptafluoroisopropyl)ketone,
15 Bis(hexafluoroisopropyl)maleate, Bis(hexafluoroisopropyl)itaconate, Bis[2-iodo-3-
(perfluoroctyl)propyl]adipate, Bis(pefluoroctyl)itaconate, Bis(perfluoroctyl)maleate,
Bis(2,2,2-trifluoroethyl)itaconate, Bis(2,2,2-trifluoroethyl)maleate, 1H,1H-2,5-
Bis(trifluoromethyl)-3,6-Dioxaundecafluorononanol, 3,3-Bis(trifluoromethyl)-3-
Hydroxypropionic Acid, 2,2 Bis (trifluoromethyl) Propionic Acid, n-Butyl-1,1,2,2-
20 Tetrafluoroethyl Ether, n-Butyl Trifluoroacetate, tert-Butyl Trifluoroacetate,
1,1,1,5,5,6,6,7,7,7-Decafluoro-2,4-Heptanedione, 1H,1H,6H-Decfluorohexan-1-ol, 2H,3H-
Decafluoropentane, Diethyl Difluoromalonate, 2,2-Difluoroethanol, 2,2-Difluoroethyl
acetate, 2,2-Difluoroethylalamine, DL-4,4-Difluoroglutamic acid, 2,2-Difluoromalonamide,
Difluoromethyl, 2,2,3,3,3-Pentafluoropropyl Ether, Difluoromethyl 2,2,2-Trifluoroethyl
25 Ether, Difluoromethyl 2,2,2-Trifluoroethyl Ether, 1,3-Difluoro-2-propanol, Dimethyl,
Hexafluoroglutarate, Dimethyl Octafluoroadipate, Dimethyl Perfluoroazelate, Dimethyl
Perfluoro-1,10-decanedicarboxylate, Dimethyl Perfluorosebacate, Dimethyl
Perfluorosuberate, Dimethyl Tetrafluorosuccinate, Dimethyl 2,2,2-Trifluoropropionyl
Carbinol, 4-Ethoxy-1,1,2-Trifluorobut-1-ene, Ethyl 3-Amino-4,4,4-trifluorocrotonate,
30 Ethyl Ethoxymethylene-3-oxo-4,4,4-trifluorobutyrate, Ethyl 4-Fluoro-3-methyl-2-
pentenoate, Ethyl 2-Fluoropropionate, Ethyl Heptafluorobutyrate, Ethyl
Heptafluorobutyrylacetate, Ethyl 3-Hydroxy-4,4,4-trifluorobutyrate, Ethyl 2-Methyl-3-
hydroxy-4,4,4-trifluorobutyrate, Ethyl Pentafluoropropionate, Ethyl Perfluoroheptanoate,
Ethyl Perfluoro-n-dodecanoate including all compounds like C_nF_{2n+1}CO₂CH₂CH₃, n= 4
35 to 16 (some H substitution possible in the CF chain, and double bonds), Ethyl Perfluoro-n-
dodecanoate, Ethyl 7H-Perfluoroheptanoate, Ethyl Perfluorononanoate, Ethyl 9H-
Perfluorononanoate, Ethyl Perfluorooctanoate, Ethyl Perfluoropentanoate, Ethyl 5H-
Perfluoropentanoate, Ethyl 11H-Perfluoroundecanoate, Ethyl 1,1,2,2-Terafluoroethyl

Ether, Ethyl 4,4,4-Trifluorobutyrate, Ethyl 3-(Trifluoromethyl)crotonate, Ethyl 4,4,4-Trifluoro-3-(trifluoromethyl)crotonate, Fluorinert (FC40, FC430, FC70, FC71, FC72, FC77, FC84, FC87, FC104, FC6001, FC6003), DL-2-Fluoro-3-alanine, 2-Fluoroethanol, D-Erythro-4-Fluoroglutamic Acid, 2-Fluoroethyl Methacrylate, DL-4-Fluoroglutamic Acid, L-Erythro-4-Fluoroglutamic Acid, D-Threo-4-Fluoroglutamic Acid, DL-Threo-4, Fluoroglutamic Acid, L-Threo-4-Fluoroglutamic Acid, DL-Erythro-4-Fluoroflutamine, L-Erythro-4-Fluoroglutamine, DL-Threo-4-Fluoroglutamine, DL-Erythro-4-Fluoroisoglutamine, L-Erythro-4-Fluoroisoglutamine, DL-Threo-4-Fluoroisoglutamine, 3-Fluoro-DL-Norleucine, Flutec (PP1, PP2, PP3, PP9, PP10, PP11, PP25, PP50), Fomblin 10 (M, Y (L-Vac), Y (H-Vac), Z15, MF402, ZDOL), Galden (HT70, HT85, HT90, HT100, HT110, HT135, HT200, HT230, HT250, HT270), 1H,1H Heptafluorobutan-1-ol, 1H,1H-Heptafluorobutyl Acetate, Heptafluorobutyramide, Heptafluorobutyric Acid, Heptafluorobutyric Anhydride, 4,4,5,5,6,6,6-Heptafluorohexanoic Acid, 4,4,5,5,6,6,6-Heptafluorohexan-1-ol, 4,4,5,5,6,6,6-Heptafluorohex-2-en-1-ol, Heptafluorosiopropyl 15 Methyl Ether, 1,1,1,3,5,5-Heptafluoropentane-2,4-dione, Heptafluoropenta-2-ol, 2-Heptafluoropropoxy-2,3,3,3-tetrafluoropropan-1-ol, Heptafluoropropyl Methyl Ether, Heptafluoropropyl 1,2,2,2-tetrafluoroethyl Ether, Heptafluoropropyl Trifluorovinyl Ether, 2,2,3,4,4,4-Hexafluorobutan-1-ol, 2,2,3,3,4,4-Hexafluorobutan-1-ol, 2,2,3,4,4,4, Hexafluorobutyl Difluoromethyl Ether, 2,2,3,4,4,4-Hexafluorobutyl Methacrylate, 20 Hexafluoroglutaramide, Hexafluoroglutaric Acid, Hexafluoroisopropanol, 1,1,1,3,3,3-Hexafluoroisopropyl Acrylate, mono-Hexafluoroisopropyl Itaconate, mono-Hexafluoroisopropyl Maleate, 1,1,1,3,3,3-Hexafluoroisopropyl methacrylate, Hexafluoroisopropyl Methyl Ether, Hexafluoroisopropylurethane-N-ethyl Methacrylate, Hexafluoroleucine, Hexafluoro-2-methylisopropanol, Hexafluoro-1,5-pentanediol, 25 3,3,4,5,5,5-Hexafluoropentan-2-ol, 1,1,2,3,3,3-Hexafluoropropyl Ethyl Ether, 1,1,2,3,3,3-Hexafluoropropyl Methyl Ether, 4,4,4,6,6,6-Hexafluoro-4-(trifluoromethyl)hexan-1-ol, 4,5,5,6,6,6-Hexafluoro4-(trifluoromethyl) hex-2-enoic Acid, 4,5,5,6,6,6-Hexafluoro-4-(trifluoromethyl) hex-2-en-1-ol, Hexafluoro-DL-valine, Isopropyl Trifluoroacetate, N, Methylbis(heptafluorobutyramide), Methyl Heptafluorobutyrate, Methyl 30 Heptafluoropropyl Ketone, Methyl 2,2,3,3,4,4-hexafluorobutyrate, Methyl 2-hydroxy-2-(trifluoromethyl)pen-4-enoate, N-Methyl-N, methoxytrifluoroacetamide, Methyl Nonafluorobutyl Ether, Methyl Nonafluorobutyl Ketone, Methyl 2,2,3,3,4,4,5,5-octafluoropentanoate, Methyl Pentafluorobut-3-enoate, Methyl Pentafluoropropionate, Methyl Pentafluoropropionylacetate, Methyl Perfluorodecanoate, Methyl 35 Perfluorododecanoate, Methyl Perfluorohexanoate, Methyl 7H-Perfluorohexanoate, Methyl Perfluorohexadecanoate, Methyl Perfluoro(2-methyl-3-oxahexanoate), Methyl Perfluorononanoate, Methyl Perfluorooctadecanoate, Methyl Perfluoropentadecanoate, Methyl Perfluorotetradecanoate, Methyl Perfluoro-2,5,8,11-tetramethyl-3,6,9,12-

tetraoxapentadecanoate, Methyl Perfluorotridecanoate, Methyl Perfluoroundecanoate,
Methyl 2,3,3,3-Tetrafluoropropionate, Methyl Trifluoroacetate, Methyl 4,4,4-
trifluoroacetoacetate, 2-Methyl-4,4,4-trifluorobutanol, Methyl 4,4,4-trifluorocrotonate,
Methyl 2-(trifluoromethyl), 3,3,3-trifluoropropionate, Methyl Trifluoropropenoate, Methyl
5 Trifluoropyruvate, (Nonafluoro-n-butyl)epoxide, 2-(Nonafluorobutyl)ethyl acrylate, 2-
(Nonafluorobutyl)ethyl methacrylate, 6-(nonafluorobutyl)hexanol, 3-(Nonafluorobutyl)-2-
hydroxypropyl Acrylate, 3-(Nonafluoro-n-butyl)prop-2-enol, 3-(Nonafluoro-n-butyl)1,2,-
propenoxide, 1H,1H,2H,2H-Nonafluorohexan-1-ol, 1H,1H-Nonafluoropentan-1-ol,
2,2,3,3,4,4,5,5-Octafluoro-1,6-hexanediol, 2,2,3,3,4,4,5,5-Octafluorohexane-1,6-diacrylate,
10 2,2,3,3,4,4,5,5, Octafluorohexane-1,6-diamethacrylate, 3,3,4,4,5,5,6,6-Octafluoro-1,8-
octanediol, 1H,1H,1H-Octafluoropenta-1-ol, 2,2,3,3,4,4,5,5 Octofluoro-1,6-hexanediol,
1,1,1,2,2-Pentafluorobutan-2-ol, 1,1,1,2,2-Pentafluoro-6,6-dimethyl-3,5-heptadione, 6-
(Pentafluoroethyl)hexan-1-ol, 4,4,5,5,5-Pentafluoropentan-1-ol, 2,2,3,3,3-
Pentafluoropropan-1-ol, Pentafluoropropionaldehyde Hydrate, Pentafluoropropionaldehyde
15 Methyl Hemiacetal, Pentafluoropropionamide, 2,2,3,3,3-Pentafluoropropyl Acrylate,
2,2,3,3,3-Pentafluoropropyl Methacrylate, 2,2,3,3,3-Pentafluoropropyl Methyl Ether,
2,2,3,3,3-Pentafluoropropyl 1,1,2,2-Tetrafluoroethyl Ether, 1H,1H,10H,10H-Perfluoro-
1,10-decanediol, 1H,1H-Perfluorodecan-1-ol, 1H,1H,2H,2H-Perfluorodecan-1-ol,
1H,1H,2H,2H-Perfluorodecanethiol, 1H,1H,2H,2H-Perfluorodecyl Acrylate,
20 1H,1H,2H,2H-Perfluorodecyl Methacrylate, 3-(Perfluoro-n-decyl)prop-2-enol, 3-
(Perfluoro-n-decyl)-1,2-propenoxide, 1H,1H-Perfluoro-(3,7-dimethyloctan-1-ol), 2H-
Perfluoro-(5,8-dimethyl-3,6,9-trioxadodecane), 1H,1H,12H,12H-perfluoro-1,12-
dodecanediol, 1H,1H-Perfluorododecan-1-ol, 1H,1H,2H,2H-Perfluorododecan-1-ol,
1H,1H,2H,2H-Perfluorododecyl Acrylate, 1H,1H,2H,2H-Perfluorododecyl Methacrylate,
25 7H-Perfluoroheptanal, 7H-Perfluoro-1,1-heptanediol, Perfluoroheptanoic Anhydride,
1H,1H-Perfluoroheptan-1-ol, 1H,1H,7H-Perfluoroheptan-1-ol,
Perfluoroheptoxy poly(propyloxy) Acrylate, Perfluoroheptoxy poly(propyloxy)
Methacrylate, 1H,1H,7H-Perfluoroheptyl Methacrylate, 1H,1H-Perfluorohexadecan-1-ol, 3
Perfluorohexy-2-Hydroxypropyl Methacrylate, 2-(Perfluoro-n-hexyl)acetaldehyde
30 Dimethyl Acetal, 3-Perfluorohexyl-2-hydroxypropyl Acrylate, 3-Perfluorohexyl-2-
hydroxypropyl Methacrylate, 3-(Perfluorohexyl)propan-1-ol, 3-(Perfluoro-n-hexyl)prop-2-
enol, 3-(Perfluoro-n-hexyl)-1,2-propenoxide, 11-(Perfluoro-n-hexyl)undecanol, 11-
(Perfluoro-n-hexyl)undec-10-enol, 6, (Perfluorosiopropyl)hexan-1-ol, 3-(Perfluoro-3-
methylbutyl)-2-hydroxy Propyl Acrylate, 3-(Perfluoro-3-methylbutyl)-2-hydroxy Propyl
35 Methacrylate, 1H,1H,2H,2H-Perfluoro-9-methyldecan-1-ol, 2-(Perfluoro-9-
methyldecyl)ethyl Acrylate, 2H-perfluoro-5-methyl-3,6-dioxanonane, 1H,1H,2H,2H-
Perfluoro-11-methyldodecan-1-ol, Perfluoro-(2-methylhept-3-ene-5-one), 1H,1H,2H,2H,
Perfluoro-5-methylhexan-1-ol, 2-(Perfluoro-5-methylhexyl)ethyl Acrylate, 2 (perfluoro-5-

methylhexyl)ethyl Methacrylate3-(Perfluoro-5-methylhexyl)-2-hydroxypropyl Acrylate, 3-(Perfluoro-5-methylhexyl)-2-hydroxypropyl Methacrylate, 1H,1H,2H,2H,-Perfluoro-7-methylocatn-1-ol, 2-(Perfluoro-7-methyloctyl)ethyl Acrylate, 2-(Perfluoro-7-methyloctyl)ethyl Methacrylate, 6-(Perfluoro-7-methyloctyl)hexanol, 3-(Perfluoro-7-methyloctyl)-2-hydroxypropyl Acrylate, 3-(Perfluoro-7-methyloctyl)-2-hydroxypropyl Methacrylate, 1H,1H,2H,3H,3H-Perfluoro-1,2-nonanediol, 1H,1H,9H,9H-Perfluoro-1,9-nonanediol, 1H,1H-Perfluorononan-1-ol, 1H,1H,9H-perfluorononan-1-ol, 1H,1H,9H-Perfluoronon-1-ene, 1H,1H,9H-Perfluorononyl Acrylate, 1H,2H,9H-Perfluorononyl Methacrylate, 1H,1H-Perfluoroctadecan-1-ol, 1H,1H,8H,8H-Perfluoro-1,8-octanediol, n-Perfluoroctanoic acid Ammonium Salt, 1H,1H-Perfluoroctan-1-ol, 1H,1H,2H,2H-Perfluoroctan-1-ol, 1H,1H,8H-Perfluoroctan-1-ol, Perfluoroctoxy-poly(isobutoxy)-2-chloropropoxy-1,2-propyl Diacrylate, 2-(Perfluoro-n-octyl)acetaldehyde, 2-(Perfluoro-n-octyl)acetaldehyde Diethyl Acetate, Perfluoroctyl Acrylate, 1H,1H-Perfluoroctyl Acrylate, 1H,1H,2H,2H-Perfluoroctyl Acrylate, 6-(Perfluoroctyl)hexanol, 3-(Perfluoroctyl)-2-hydroxypropyl Acrylate, 3-(Perfluoroctyl)-2-hydroxypropyl Methacrylate, mono-Perfluoroctyl Itaconate, mono-Perfluoroctyl Maleate, Perfluoroctyl Methacrylate, 1H,1H-Perfluoroctyl Methacrylate, 3-(Perfluoroctyl)propanol, 3-(Perfluoroctyl)prop-2-enol, 11-(Pefluoro-n-octyl)undec-10-en-1-ol, 1H,1H,5H,5H-Perfluoropentyl-1,5-dimethacrylate, Pefluoropolyether linear & PFO-XR75, Perfluorosebacic Acid, 1H,1H-Perfluorotetradecan-1-ol, 1H,1H,13H-Perfluorotridecan-1-ol, Perfluoro-2-trifluoromethyl-4-oxanonane, Perfluoro-(3,5,5-trimethylhexanoic)acid, 1H,1H-Perfluoro(3,5,5-trimethylhexan-1-ol), 2H-Perfluoro-(5,8,11-trimethyl-3,6,9,12-tetraoxatetradecane), 1H,1H,2H,3H,3H-Perfluoro-1,2-undecanediol, Perfluoroundecanoic Acid, 1H,1H-Perfluoroundecan-1-ol, 1H,1H,11H-Perfluoroundecan-1-ol, 1H,1H,11H-Perfluoroundecyl Acrylate, 1H,1H,11H-Perfluoroundecyl Methacrylate, Polyperfluoroethylene glycol Diacrylate, Polyperfluoroethylene glycol Dimethacrylate, Sodium Heptafluorobutyrate, Sodium Pentafluoropropionate, 2,2,3,3-Tetrafluoro-1,4-butanediacrylate, 2,2,3,3-Tetrafluoro1,4,butanedimethacrylate, 1,1,3,3-Tetrafluorodimethyl Ether, 1,1,2,2-Tetrafluoroethyl 2,2,3,3-tetrafluoropropyl Ether, 1,1,2,2, Tetrafluoroethyl 2,2,2-trifluoroethyl Ether, 1122 Tetrafluoroethyl 222 Trifluoroethyl Ether, 1,2,2,2-Tetrafluoroethyl Trifluoromethyl Ether, 4,5,5,5-Tetrafluoro-4-(heptafluoropropoxy)pentanoic Acid, 4,5,5,5-Tetrafluoro-4-(heptafluoropropoxy)pentan-1-ol, Tetrafluorosuccinic acid, 4,5,5,5-Tetrafluoro-4-(trifluoromethoxy)pentan-1-ol, 4,5,5,5-Tetrafluoro-4-(trifluoromethyl)pent-2-en-1-ol, N-(N-Trifluoroacetyl-L-cysteinyl)glycine Methyl Ester, DL-3,3,3-Trifluoro-2-alanine, 4,4,4-Trifluorobutan-1-ol, 1,1,1-Trifluorobutan-2-one, 4,4,4-Trifluorobutan-2-one, 4,4,4-Trifluorobut-2-en-1-ol, 1,1,2-Trifluoro-2-chloroethyl 2,2,2-trifluoroethyl ether, 4,4,4-

Trifluorocrotonamide, 4,4,4-Trifluoro-3,3-dimethoxybutanol, 2,2,2-Trifluoroethanol, 2,2,2-Trifluoroethyl Butyrate, 1,2,2-Trifluoroethyl Trifluoromethyl Ether, 1,1,1-Trifluoro-2,4-hexanedione, Beta-Trifluoromethylcrotonic Acid, DL-2-(Trifluoromethyl)leucine, DL-2-(Trifluoromethyl)norleucine, DL-2-(Trifluoromethyl)norvaline, 2-

5 (Trifluoromethyl)propan-2-ol, 6,6,6-Trifluoronorleucine, 5,5,5-Trifluoronorvaline, 1,1,1-Trifluoropropan-2-ol, 3,3,3-Trifluoropropan-1-ol, 1,1,1-Trifluoro-2-propyl Acetate, 4,4,4-Trifluoro-3-(trifluoromethyl)butan-1-ol, 2-Allyl Hexafluorosopropanol, Butyl Difluoroacetate, n-Butyl Pentafluoropropionate, tert-Butyl Pentafluoropropionate, N,N-Diethyl-2,3,3,3-tetrafluoropropionamide, 22 Difluoroethyl Trifluoromethyl Ether, 1-

10 (Ethoxy)nonafluorobutane, 3-Fluoropropan-1-ol, 3H-Heptafluoro-2,2,4,4-tetrahydroxy Pentane, 2,2,3,3,4,4-Hexafluoro-1,5-pentyl Diacrylate, 1,1,2,3,3,3-Hexafluoropropyl 2,2,2-trifluoro Ethyl Ether, Methyl 2,2-Difluoro-3-oxopentanoate, Methyl 2, Methoxytetrafluoropropionate, Methyl Perfluoro-2,5,8,11-tetramethyl-3,6,9,12-tetraoxapentadecanoate, Methyl 3,3,3-Trifluoro-DL-lactate, 3,3,4,4,4-Pentafluorobutan-2-one, Pentafluorodiethyl Ether, Pentafluoroethyl Methyl Ether, 2,2,3,3,3-Pentafluoropropyl Trifluoromethyl Ether, 2-(Perfluoroalkyl)ethanol, Perfluoroallylfluorosulphate, Perfluoro-2,5,8,11,14,17,20-heptamethyl-3,6,9,12,15,18-hexaoxahenelcosanoyl Fluoride, Mono-Perfluoroctyl Itaconate, 2H-Perfluoro-5,8,11,14,17-pentamethyl-3,6,9,12,15,18-hexaoxahenicosane, Perfluoropolyether Dinitrile,

20 Polyfluoropolyethyleneacrylate, Polyfluoropolyethylenemethacrylate, 2,2,2-Trifluoroethyl Trifluoromethyl Ether, Perfluorodecaline, Perfluoroctyl Bromide, di-Chloro-octyl Bromide or 1H,1H,5H Octafluoro-1-pentanol.

9. A pharmaceutical aerosol formulation as claimed in any preceding claim, wherein the
25 excipient is a PEG co-polymer.

10. A pharmaceutical aerosol formulation as claimed in any preceding claim, wherein the
excipient is a PEG-phospholipid.

30 11. A pharmaceutical aerosol formulation as claimed in any preceding claim, wherein the
excipient is selected from:

Acrylidone 1005, Crodesta F160, Methoxy PEG Amine, Methoxy PEG carboxymethyl, 4-arms PEG, Cholic acid, MYRJ 52 P, APG-810-XL, APG-1014-XL, Glucapon 215, Glucapon 600, Brij 52, Gum Xanthan, Salicylic Acid, D-Lactose monohydrate, α Lactose monohydrate, Lecithin egg, Carrageean, Sokalan CO5, Eudragit RLPO, Eudragit RSPO, Eudragit E100, Eudragit S100, Eudragit L100, Poly (DL-lactide coGlycolide), Gantrez S-97 BF, Gantrez AN-119, Gantrez AN-169, Myristic acid, Poly (lactide EO Lactid), Poly

(methyl methacrylate- β -ethylene oxide), Lactose, Carboxymethyl cellulose Sodium Salt, 1-O-n-Octyl β D glucopyranoside, AOT DI-CF4H, Dioctyl-sulfosuccinate sodium salt (AOT), Phospholipon 100, Crodesta F10, Crodesta SL 40, APG 3399, Methoxy-PEG-DSPE MW 2000, Methoxy-PEG-DSPE MW 5000, N Dodecyl β D Maltoside, N Octyl β D Glucopyranoside, α cyclodextrin, β cyclodextrin hydrate, γ cyclodextrin hydrate, γ cyclodextrin, γ cyclodextrin hydrate, Deoxycholic acid, Taurocholic acid, D-Mannitol, Poly (Methyl Methacrylate), Montanov 202, Montanov 68 EC, n Dodecyl β D Glucopyranoside, N Decyl β D Glucopyranoside, n Decyl β D Maltopyranoside, Glucamate DOE-120, Glucate SS, Glucamate SSE-20, Glucam DOE-120, Glucam P10, 10 Glucam E20, Glucam P20 disteared, Glucam P20, Glucquat 125, Brij 30, Brij 96, Crodasinic LS 30, Crossential L99, Copolymer VC 713, Copolymer 958, Glucopon 650 EC, α Tocopherol, PVP K30, K25 and Plasdone K-29/32, PEG 600 and 1000, Three-Arm Poly (ethylene glycol), lactose based compounds (eg Poly (lactide -co glycolide), Lactitol, Lactose, Cellulose 15 based compounds (e.g. Carboxymethylcellulose, Cellulose, Hydroxypropyl cellulose), Fatty acids (e.g. Castor oil), PEG and derivatives (e.g. Star PEG), Sugar compounds (e.g. Alkyl polyglucosides, Methyl glucosides, Sucrose esters, such as Berol AG6202, Glucopon chemical range, Montanov 68, Montanov 202, Grilloten LSE87, Crodesta chemical range), Poly(ethylene Oxide) compounds (e.g. Hydroxy terminated Three-Arm Polyethylene 20 oxide, Hydroxy terminated Eight-Arm Polyethylene oxide, Carboxy terminated Eight-Arm Polyethylene Oxide, 4 Arms Star Polyethylene Oxide, Poly(methyl methacrylate-b-ethylene oxide), Poly(t-butyl methacrylate-b-ethylene oxide), Poly(lactide-ethylene oxide-lactide triblock copolymer), Ω -Diacrylonyl terminated poly(lactide-ethylene oxide-lactide) triblock copolymer, Poly(lactone- β -ethylene oxide- β -lactone) triblock copolymer, 25 Poly(ethylene oxide- β -caprolactone), Poly(ethylene oxide- β -propylene oxide) also known as PEO-PPO copolymers, Poly(methyl methacrylate- β -ethylene oxide) also known as PMMA-PEO copolymers)). Further examples include Citric acid, Dibutyl Sebacate, Edetic acid, Glyceryl monooleate & monostearate, Glycofinol, Crodamol chemical range, Maltitol, Maltodextrin, Triglyceride, Polymethacrylate, Polyosyethylene alkyl ether, 30 Sodium citrate dihydrate, Sorbitol, Mirj and Brij chemical range, Pluronic chemical range, Acrylidone 1005, Fluorinated AOT with different degrees of fluorination, Cholic acid, Copolymer 958, Copolymer VC713, Crossential L99, Crodasinic LS30, AOT Sodium salt, Phospholipon 100H, Salycilic acid, Sokalan CO5, Poly (lactide co glycolide), Poly(ethylene- β -methyl methacrylate), Poly(ethylene- β -2-vinyl pyridine), 35 Poly(ethylene- β -4-vinyl pyridine), Poly(methyl methacrylate- β -sodium acrylate), Poly(methyl methacrylate- β -sodium methacrylate), PEG derivative compounds (Amino acid-PEG, Carboxyl-PEG copolymers, Methoxy PEG amine, Methoxy PEG carboxymethyl, Branched PEG 4 arms, star PEG, PEG-PLA-PEG triblock copolymer),

sugar branched cyclodextrins derivatives, PEO cyclodextrins derivatives, and Dendrimer-PEO-Dendrimer triblock-copolymers, Methoxy-PEG-DSPE MW 5000, Eudragit E100, Glucamate DOE 120, Methoxy-PEG-DSPE MW 2000, Acrylidone 1005, Crodesta F160, Methoxy PEG Amine, Methoxy PEG carboxymethyl, 4 arms PEG, Cholic acid, MYRJ 52
5 P, APG-810-XL, APG-1014-XL, Glucopon 215, Glucopon 600, Brij 52, Gum Xanthan, Salicylic Acid, D-Lactose monohydrate, α Lactose monohydrate, Lecithin egg, Carrageean, Sokalan CO5, Eudragit RLPO, Eudragit RSPO; Eudragit E100, Eudragit S100, Eudragit L100, Poly (DL-lactide coGlycolide), Gantrez S-97 BF, Gantrez AN-119, Gantrez AN-169, Myristic acid, Poly (lactide EO Lactid), Poly (methyl methacrylate- β -ethylene oxide), Lactose, Carboxymethyl cellulose Sodium Salt, 1-O-n-Octyl β D
10 glucopyranoside, AOT DI-CF4H, Dioctyl-sulfosuccinate sodium salt (AOT), Phospholipon 100, Crodesta F10, Crodesta SL 40, APG 3399, Methoxy-PEG-DSPE MW 2000, Methoxy-PEG-DSPE MW 5000, N Dodecyl β D Maltoside, N Octyl β D
Glucopyranoside, α cyclodextrin, β cyclodextrin hydrate, β cyclodextrin, gamma
15 cyclodextrin hydrate, gamma cyclodextrin, gamma cyclodextrin hydrate, Deoxycholic acid, Taurocholic acid, D-Mannitol, Poly (Methyl Methacrylate), Montanov 202, Montanov 68 EC, n Dodecyl β D Glucopyranoside, N Decyl β D Glucopyranoside, n Decyl β D
Maltoxyranoside, Glucamate DOE-120, Glucate SS, Glucamate SSE-20, Glucam DOE-
120, Glucam P10, Glucam E20, Glucam P20 disteared, Glucam P20, Glucquat 125, Brij
20 30, Brij 96, Crodasinic LS 30, Crossential L99, Copolymer VC 713, Copolymer 958, Glucopon 650 EC, α Tocopherol, PVP K30, K25 and Plasdone K-29/32, PEG 600 and 1000, Three-Arm Poly (ethylene glycol).

12. The use of a polar fluorinated molecule in conjunction with an excipient to reduce
25 deposition and creaming of a pharmaceutical aerosol formulation, and obtain a very fine stable suspension comprising a hydrofluoroalkane propellant having dispersed therein drug particulates.

13. An aerosol can containing a formulation as claimed in any of claims 1 to 11.
30

14. A can according to claim 13 which is made of metal.

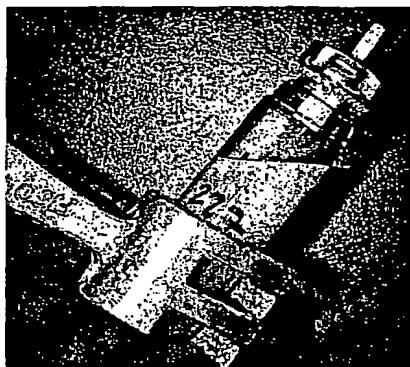
15. An aerosol can as claimed in claim 13 or 14 wherein the internal surfaces of the can are coated with a fluoropolymer.

35

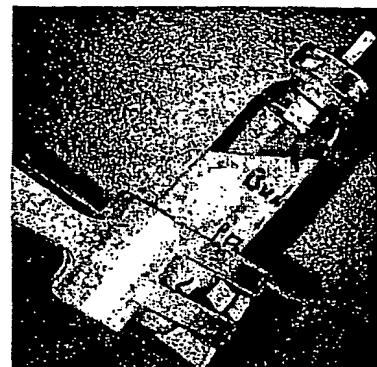
16. A pharmaceutical aerosol formulation as claimed in any of claims 1 to 11 for use in therapy.

17. A pharmaceutical aerosol formulation as claimed in any of claims 1 to 11 for use in the treatment of asthma, rhinitis or COPD.

18. A method for the treatment of a patient in need of therapy, comprising administering to said patient a therapeutically effective amount of the pharmaceutical aerosol formulation as claimed in any of claims 1 to 11.

Figure 1/10

**Figure 1 (Budesonide with
Methoxy-PEG-DSPE MW 5000
in 4HPFOH and HFA 227)**



**Figure 2 (Budesonide with
Methoxy-PEG-DSPE MW 5000
in 4HPFOH and HFA 134a)**



**Figure 3 (Formoterol
Fumarate Dihydrate with
Methoxy-PEG-DSPE MW 5000
in 4HPFOH and HFA 227)**



**Figure 4 (Formoterol
Fumarate Dihydrate with
Methoxy-PEG-DSPE MW 5000
in 4HPFOH and HFA 134a)**

Figure 2/10

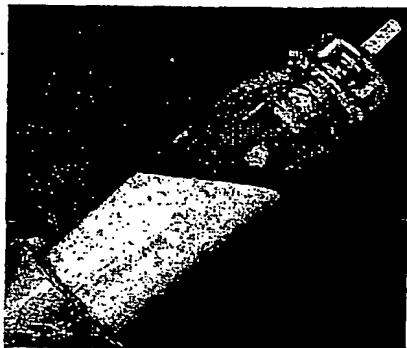


Figure 5



Figure 6

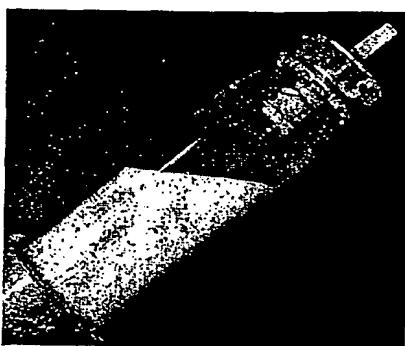


Figure 7



Figure 8



Figure 9



Figure 10

BEST AVAILABLE COPY

Figure 3/10

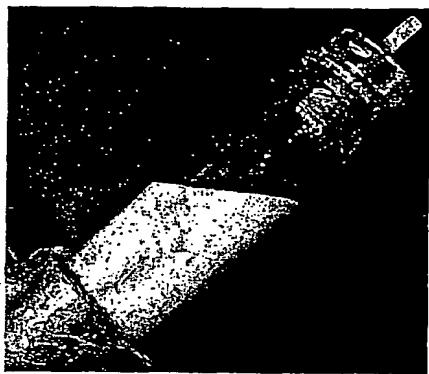


Figure 11

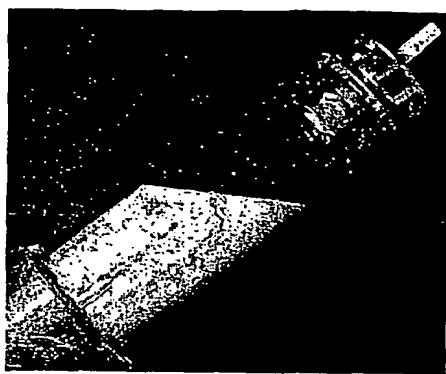


Figure 12

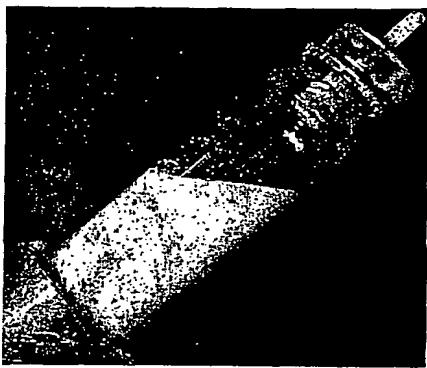


Figure 13



Figure 14



Figure 15

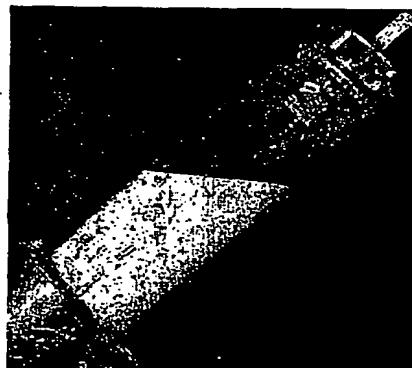


Figure 16

Figure 4/10

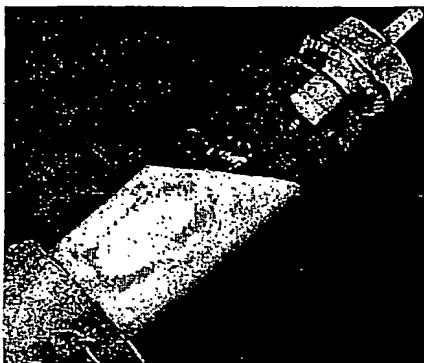


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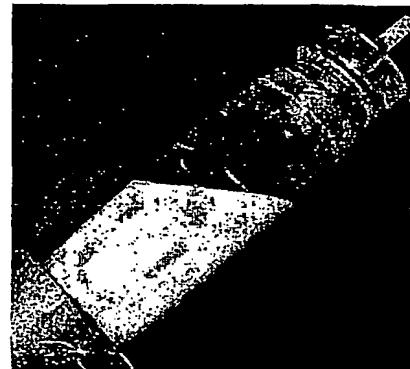


Figure 18



Figure 19

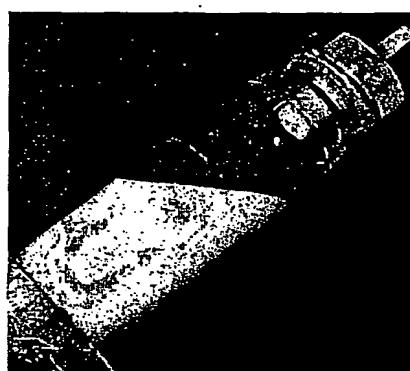


Figure 20



Figure 21

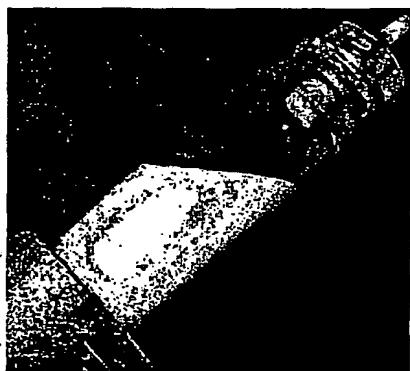


Figure 22

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Figure 5/10

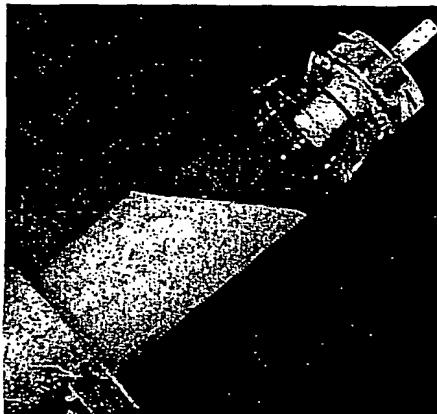


Figure 23

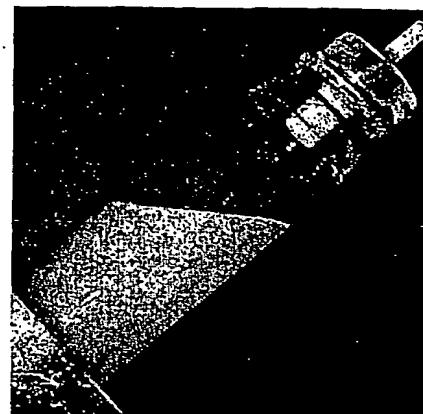


Figure 24

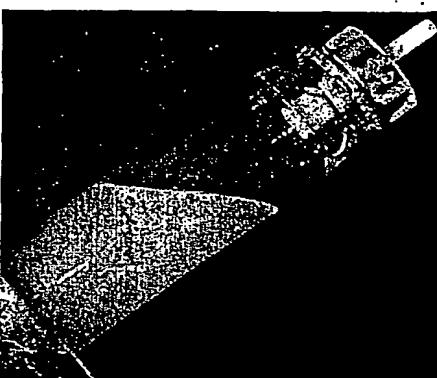


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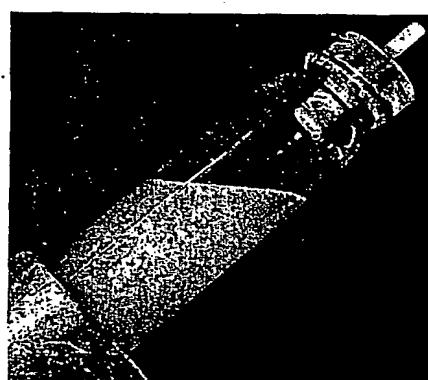


Figure 26

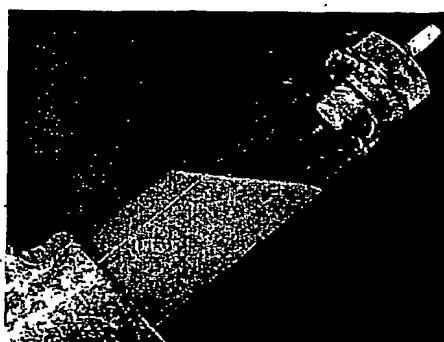


Figure 27

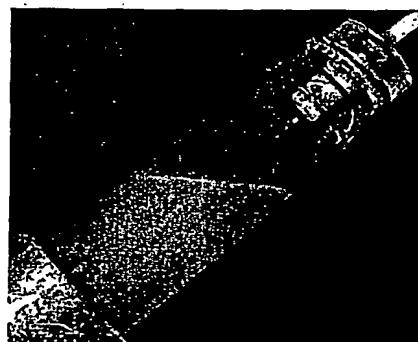


Figure 28

Figure 6/10



Figure 29



Figure 30



Figure 31



Figure 32

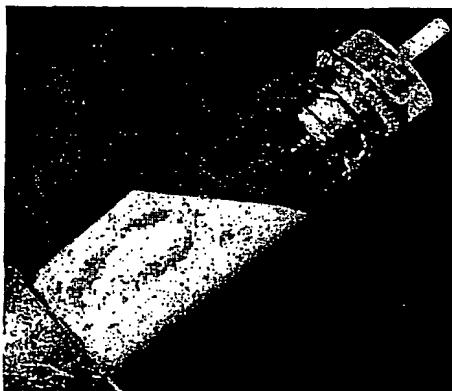


Figure 33



Figure 34

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Figures 7/10



Figure 35



Figure 36



Figure 37



Figure 38



Figure 39



Figure 40

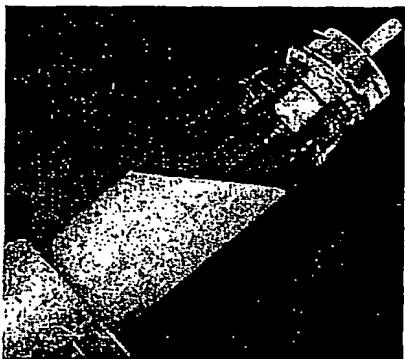
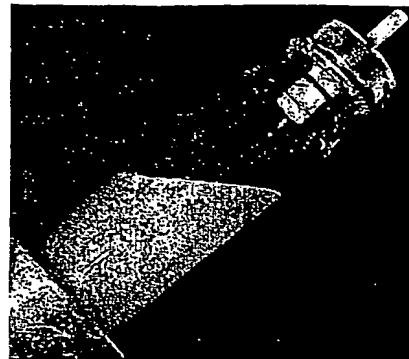
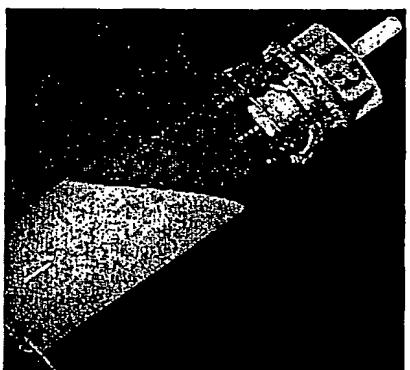
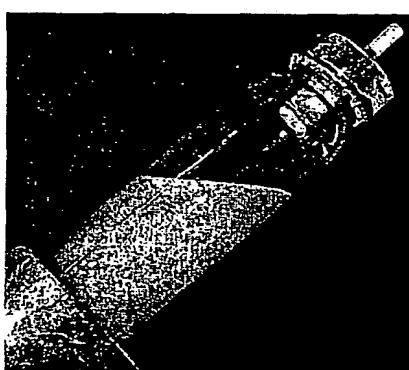
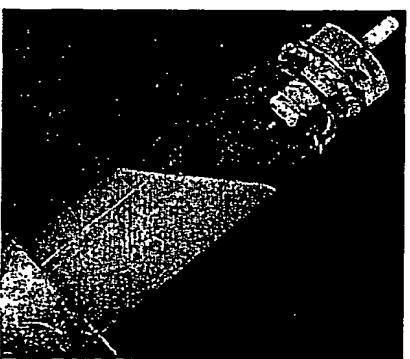
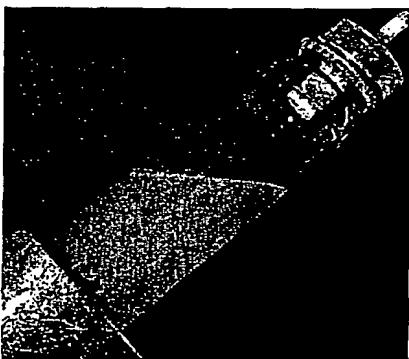
Figure 8/10**Figure 41****Figure 42****Figure 43****Figure 44****Figure 45****Figure 46**

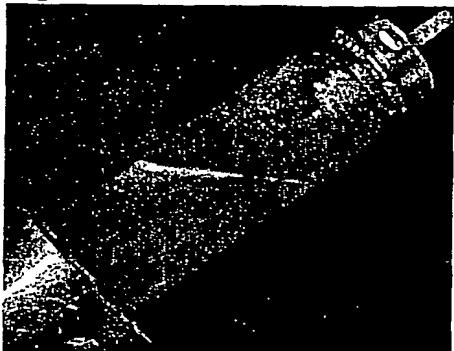
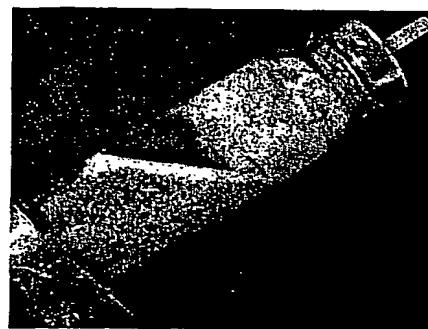
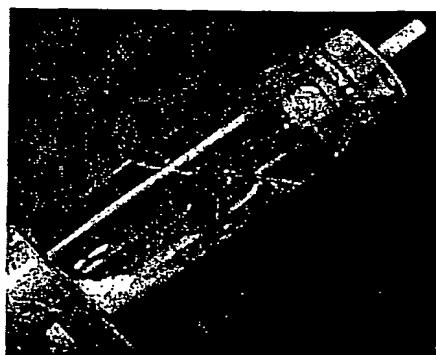
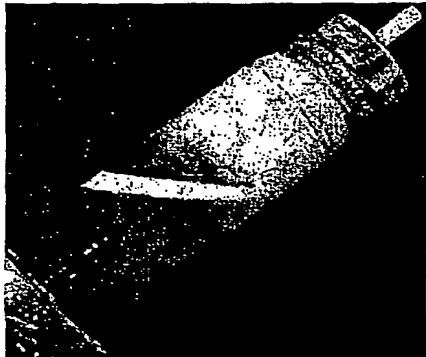
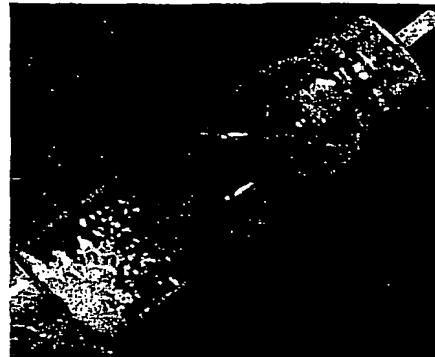
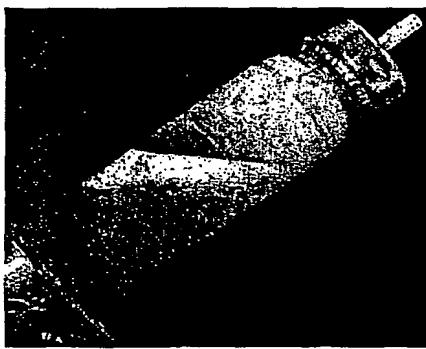
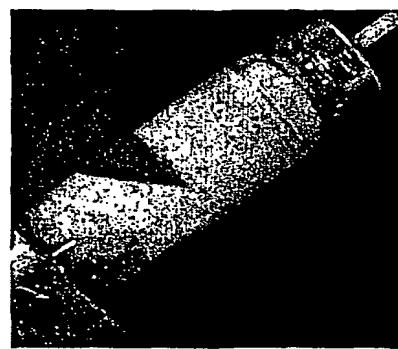
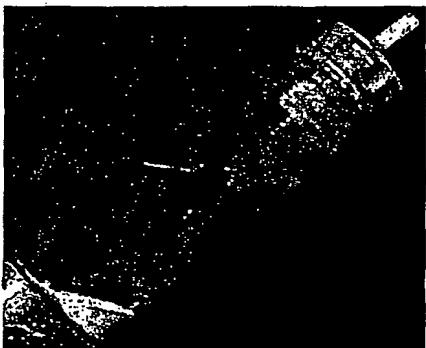
Figure 9/10**Figure 47 (Formoterol Fumarate Dihydrate in HFA 227)****Figure 48 (Formoterol Fumarate Dihydrate in HFA 134a)****Figure 49 (Formoterol Fumarate with PEG 1000 and PVP K25 in a HFA 227 and HFA 134a mix)****Figure 50 (Terbutaline Dihydrate sulphate in HFA 227)****Figure 51 (Terbutaline Sulphate in HFA 134a)****Figure 52 (Terbutaline with PEG 600 and PVP K30 in HFA 277)**

Figure 10/10**Figure 53 (Budesonide in HFA 227)****Figure 54 (Budesonide in HFA 134a)****Figure 55 (Budesonide with PEG 1000 and PVP K25 in HFA 277)****Figure 56 (Viozan® in HFA 227)****Figure 57 (Viozan® in HFA 134a)****Figure 58 (Viozan® with PEG 600 and PVP K30 in HFA 277)**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01606

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/12, A61K 9/72, A61K 47/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO INTERNAL, WPI DATA, CA DATA, EMBASE, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 6149892 A (BRITTO), 21 November 2000 (21.11.00), column 1 - column 2; column 3, line 42 - line 46, and the examples --	1-18
X	US 5849265 A (LI-BOVET ET AL), 15 December 1998 (15.12.98), column 5 - column 6; column 7, line 39 - line 46, and the examples --	1-18
X	WO 9111173 A1 (FISONS PLG), 8 August 1991 (08.08.91), see especially pages nos. 6-7, the claims and the abstract --	1-18

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

15 November 2001

Date of mailing of the international search report

16-11-2001

Name and mailing address of the ISA/
Swedish Patent Office
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Facsimile No. + 46 8 666 02 86

Authorized officer

INGRID FALLENIUS/BS
Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No. PCT/SE 01/01606
--

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Anesth Analg, Volume 88, 1999, Edmond I Eger II et al: "Minimum Alveolar Anesthetic Concentration of Fluorinated Alkanols in Rats: Relevance to Theories of Narcosis", pages 867-876 --	1-18
A	US 3557294 A (ROBERT E. A. DEAR ET AL), 19 January 1971 (19.01.71) -- -----	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01606

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **18**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet*
2. Claims Nos.: **1-18**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see next sheet**
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01606

*
Claim no. 18 relates to a method of treatment of the human or animal body by therapy. Rule. 39.1.(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the composition.

**

Present claims 1-18 relate to an extremely large number of possible formulations. In fact, the claims contain so many options that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application that appear to be clear and concise, namely the formulations recited in the examples.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/10/01

International application No.

PCT/SE 01/01606

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US	6149892	A 21/11/00	AU	718851 B	20/04/00
			AU	5481296 A	30/10/96
			BG	102023 A	31/07/98
			BR	9604979 A	09/06/98
			EE	9700372 A	15/06/98
			EP	0820414 A	28/01/98
			JP	2000513237 T	10/10/00
			NO	974738 A	11/12/97
			NZ	306281 A	29/07/99
			PL	180880 B	30/04/01
			PL	322781 A	16/02/98
			SK	139197 A	08/04/98
			AP	835 A	12/05/00
			AP	9701112 D	00/00/00
			CA	2218179 A	17/10/96
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			CZ	9703261 A	16/06/99
			HU	9800641 A	28/08/98
			TR	9701170 T	00/00/00
			WO	9632345 A	17/10/96
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US	5849265	A 15/12/98	AP	742 A	26/04/99
			AP	9700951 D	00/00/00
			AT	187063 T	15/12/99
			AU	707922 B	22/07/99
			AU	3532195 A	19/04/96
			BG	62839 B	29/09/00
			BG	101347 A	30/12/97
			BR	9509108 A	14/07/98
			CA	2200986 A	04/04/96
			CN	1168630 A	24/12/97
			CZ	286356 B	15/03/00
			CZ	9700936 A	13/08/97
			DE	69513671 D,T	06/04/00
			DK	783302 T	29/05/00
			EE	9700061 A	15/08/97
			EP	0783302 A,B	16/07/97
			SE	0783302 T3	
			ES	2140706 T	01/03/00
			FI	971279 A	26/03/97
			GB	9419536 D	00/00/00
			GR	3032245 T	27/04/00
			HU	77377 A	28/04/98
			JP	10506887 T	07/07/98
			MD	970134 A	28/02/99
			NO	971422 A	23/05/97
			NZ	292995 A	28/10/98
			PL	181453 B	31/07/01
			PL	319342 A	04/08/97
			SI	783302 T	00/00/00
			SK	39397 A	08/10/97
			WO	9609816 A	04/04/96
<hr/>					

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/10/01

International application No.

PCT/SE 01/01606

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9111173 A1	08/08/91	AT 125153 T CA 2074495 A DE 69111426 D,T DK 513127 T EP 0513127 A,B SE 0513127 T3 ES 2075956 T GB 9002351 D GR 3017611 T IE 67185 B IE 910289 A IL 97065 A JP 2858948 B JP 5503523 T MX 24390 A NZ 236948 A PT 96639 A,B ZA 9100696 A GB 9023655 D GB 9026476 D	15/08/95 03/08/91 18/01/96 30/10/95 19/11/92 16/10/95 00/00/00 31/01/96 06/03/96 14/08/91 25/01/94 17/02/99 10/06/93 01/04/93 26/08/92 31/10/91 30/10/91 00/00/00 00/00/00
US 3557294 A	19/01/71	NONE	